# FORMULATION AND EVALUATION OF LAMIVUDINE SUSTAINED RELEASE MATRIX TABLETS USING SYNTHETIC POLYMERS

**A Dissertation Submitted to**

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**In partial fulfillment for the award of Degree of**

**MASTER OF PHARMACY**

**(Pharmaceutics)**

**Submitted by**

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**(Accredited By "NAAC" with CGPA of 2.74 on a Four point Scale at "B" Grade)**

**MELMARUVATHUR - 603 319**

**MAY- 2012**

## CERTIFICATE

This is to certify that the dissertation entitled "**FORMULATION AND EVALUATION OF LAMIVUDINE SUSTAINED RELEASE MATRIX TABLETS USING SYNTHETIC POLYMERS**" submitted to The Tamil Nadu Dr. M.G.R. Medical University in partial fulfillment for the award of the Degree of the Master of Pharmacy (Pharmaceutics) was carried out by **K. KAMARAJ (Register No. 26106003)** in the Department of Pharmaceutics under my direct guidance and supervision during the academic year 2011-2012.

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## CERTIFICATE

This is to certify that the dissertation entitled "**FORMULATION AND EVALUATION OF LAMIVUDINE SUSTAINED RELEASE MATRIX TABLETS USING SYNTHETIC POLYMERS**" the bonafide research work carried out by **K. KAMARAJ (Register No. 26106003)** in the Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, Melmaruvathur which is affiliated to The Tamil-Nadu Dr. M.G.R. Medical University under the guidance of **Dr. S. SHANMUGAM, M. Pharm., Ph.D.** Professor, Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, Melmaruvathur.

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*Dedicated to*

*My beloved*

*Parents & Friends…*

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**K.KAMARAJ**

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# ABBREVIATION AND MEANING

| | |
|---|---|
| % | Percentage |
| %DE | Percentage dissolution efficiency |
| µ | Micron |
| µg/ml | Microgram per millilitre |
| $^0C$ | Degree celsius |
| LAM | Lamivudine |
| $Cm^{-1}$ | Centimeter inverse |
| $C_{max}$ | Peak plasma concentration |
| DNA | Deoxy ribonucleic acid |
| DSC | Differential scanning calorimetry |
| e.g. | Example |
| EC | Ethyl cellulose |
| edn | Edition |
| F | Formulation |
| F/C | Film coated |
| FTIR | Fourier transform infrared spectroscopy |
| g/ml | gram per millilitre |
| GIT | Gastro intestinal tract |
| HCl | Hydrochloric acid |
| HPC | Hydroxy propylcellulose |

| | |
|---|---|
| HPMC | Hydroxy propyl methylcellulose |
| hrs | Hours |
| ICH | International conference on harmonization |
| IP | Indian pharmacopoeia |
| $Kg/cm^2$ | kilogram per centimeter square |
| LBD | Loose bulk density |
| MDT | Mean dissolution time |
| mg | Milligram |
| ml | Millilitre |
| ml/min | millilitre per minute |
| mm | millimeter |
| N | Normality |
| NaOH | Sodium hydroxide |
| NF | National formulary |
| nm | nanometer |
| º | Degree |
| pH | Negative logarithm of hydrogen ion |
| pKa | Dissociation constant |

| | |
|---|---|
| qs | Quantity sufficient |
| RH | Relative humidity |
| rpm | Revolution per minute |
| S.No. | Serial number |
| SD | Standard deviation |
| SR | Sustained release |
| $t_{1/2}$ | Biological half life |
| TBD | Tapped bulk density |
| $T_{max}$ | Time of peak concentration |
| USP | United states pharmacopoeia |
| UV | Ultraviolet |
| w/w | weight per weight |
| $\lambda_{max}$ | Absorption maximum |

# INTRODUCTION

# 1.INTRODUCTION

**1.1. Oral drug delivery system:** *(Banker G.S. and Rhodes C.T., 2009; Chein Y.W., 2009; http://www.pharmainfo.net)*

Oral route has been the commonly adopted and most convenient route for the drug delivery. Oral route of administration has been received more attention in the pharmaceutical field, because of the more flexibility in the designing of dosage form than drug delivery design for other routes. The oral drug delivery depends on various factors such as type of delivery system, the disease being treated, the patient, the length of the therapy and the properties of the drug. Most of the oral controlled drug delivery systems (OCDDS) relay on diffusion, dissolution, or combination of both mechanisms, to release the drug in a controlled manner to the gastro intestinal tract (GIT). The physico-chemical properties include crystal nature, solubility, partition coefficient, intrinsic dissolution, etc. dosage form characteristics are controlled and optimized with respect to the physico-chemical properties of the drug and relevant GI environmental factors. Other factors need to be considered are diseased state, the patient compliance & length of therapy. The goal of targeted oral drug delivery systems is to achieve better therapeutic success compared to conventional dosage form of the same drug. This could be achieved by improving the pharmacokinetic profile, patient convenience and compliance in therapy.

Oral route of drug delivery has been known for decades as the most to a wide extent used route of administration among all the routes that have been travel through to learn about it the systemic delivery of drugs via various pharmaceutical manufactured products of various dosage forms.

Oral route of administration has been used as either conventional or novel drug delivery system. There are many merits are there for this, not the least of which would include willingness to accept by the patient and facility of administration. Types of sustained release system employed for oral route of administration include virtually every at the present time now the theoretical mechanism for such application. This is because the manufacturing of dosage form is more flexibility, since constraint, such as sterility problem and potential damage at the site of administration are minimized. Because of this, it is easy to development of different types of dosage forms by customary those developed for oral route of administration as initial examples.

Regarding orally administered drugs, targeting is not a primary concern, and it is usually done on purpose for active component to permeate to the blood circulation and permeation through the other body tissue (the obvious exception being medication intended for local gastrointestinal tissue treatment). For this justification, most system employed the sustained release variety.

Concentration of drug level it will increasing the rate absorption region and also, increase circulating blood levels, which in turn to raise to greater concentration of active content at the site of action.

**1.2. Drawbacks of Conventional Dosage Forms:** *(Brahmankar D.M. and Jaiswal S.B., 2009; Shalin A. Modi, et al., 2011)*

1. Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.

2. The unavoidable fluctuations of drug concentration may lead to under medication or over medication.

3. A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.

4. The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.

**1.3. Sustained release drug delivery system:** *(Banker G.S. and Rhodes C.T., 2009; http://www.pharmainfo.net)*

Over past 30 year as the expanse and complication involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. There are several reasons for the attractiveness of these dosage forms. It is generally recognized that for many disease states, a substantial number of therapeutically effective compounds already exist.

The effectiveness of these drugs, however, is often limited by side effects or the necessity to administer the compound in a clinical setting, the goal in designing sustained or controlled delivery system is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery. Sustained release constitutes any dosage form that provides medication over and extended time. Controlled release, however, denotes that the system is able to provide some actual therapeutic control, whether this is of a temporal nature, spatial nature or both.

This correctly suggests that there are sustain release system that cannot be considered controlled release system. In general, the goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of drug for an extended

period this is usually accomplished by attempting to obtain zero-order release from the dosage form; zero-order release constitutes drug release from the dosage form. Sustained release systems generally do not attain this type of release and provides drug is a slow first order fashion. In recent year sustained release dosage forms continue to draw attention in the search for improved patient compliance and decreased incidence of adverse drug reactions. Sustained release technology is relatively cow field and as a consequence, research in the field has been extremely fertile and has produced many discoveries.

Sustained release, sustained action, prolonged action controlled release, extended action, timed release, depot and repository dosage forms are terms used to identify drug delivery system that are designed to achieve or prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

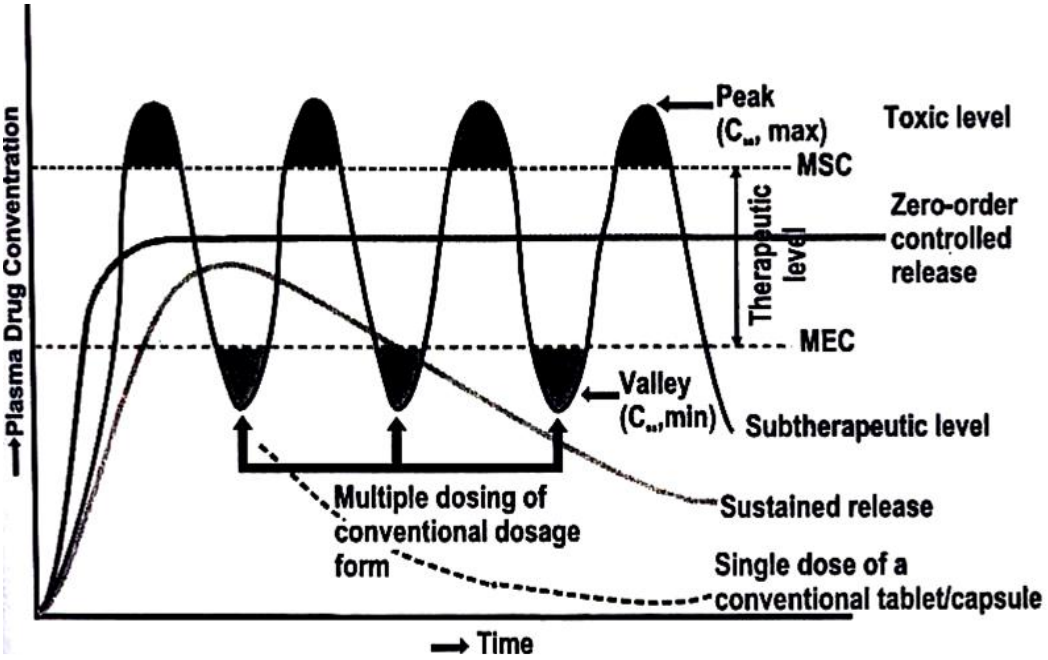



**Figure 1.1:** Plasma concentration versus time profile from conventional dosage and doses of sustained and controlled delivery formulation.

Systems that are designed as prolonged release can also be considered as attempts at achieving sustained-release delivery. Repeat action tablets are an alternative method of sustained release in which multiple doses of drug are contained within a dosage form, and each dosage is related to a periodic interval. Delayed release systems, in contrast may not be sustaining, science often function of these dosage forms is to maintain the drug within the dosage form for some time before release. Commonly the release rate of drug is not altered and does not result in sustained delivery once drug release has begun.

Successful fabrication of sustained release products is usually difficult & and involves consideration of physicochemical properties of drug, pharmacokinetic behavior of drug, route of administration, disease state to be treated and, most importantly, placement of the drug in dosage form total will provide the desired temporal and spatial delivery pattern for the drug.

The slow first order release obtained by a sustained release pre parathion is generally achieved by the release of the drug from a dosage form. In some cases in some cases, this achieved by making slow the release of drug from a dosage form. In some cases, this is accomplished by a continuous release process.

**1.3.1. Potential advantages of Sustained release drug delivery system:**

*(http://www.pharma info.net)*

1. Patient compliance due to reduction in the frequency of designing.
2. Employ minimum drug.
3. Minimize or eliminates local and systemic side effects.
4. Obtain less potentiating or deduction in drug activity with chronic use.
5. Minimize drug accumulation with chromic dosing.
6. Improves efficacy in treatment.

7. Cure or control confirm more promptly.
8. Improve control of condition i.e. reduce fluctuation in drug level.
9. Improve bioavailability of same drugs.
10. Make use of special effects, e.g. sustained release aspect for morning relief of arthritis by dosing before bedtime.

**1.3.2. Disadvantages of Sustained release drug delivery system:** (*http: //www. pharmainfo.net)*

1. They are costly.
2. Unpredictable and often poor in-vitro in-vivo correlations, dose dumping, reduced potential for dosage adjustment and increased potential first pass clearance.
3. Poor systemic availability in general.
4. Effective drug release period is influenced and limited by GI residence time.

**1.3.3. Rationale of sustained release drug delivery system:** *(Ansel H.C., 2009; Vyas S.P and Khar R.K., 2002)*

To optimizing the factor such as pharmacokinetic, pharmacodynamic and biopharmaceutical these are the rationale of sustained release dosage form, these properties of active ingredient in such a type its maximum reducing the adverse effect and controlling disease growth condition in short time period by loading less quantity of drug, when we are administered in the suitable route. Many drugs are longer action because half life and only need for once day dosing so these type of drug not for sustained or controlled release tablet to give therapeutic effect in blood and this nature of drug we can be manufacturing in immediate release tablet as like conventional tablet. However, some drugs are not long action and need multiple daily dosing to obtain the therapeutic results.

Multiple daily dosing is inconvenient for the patient, chance of missed doses, made up doses and non compliance with the regimen. When the conventional tablet which may causes variation of plasma level peaks and valley associated with the using of each dose. However, when a dose should not be administering such a manner because the obtaining result like peaks and valley give the less action of therapy. For example if a dosage form is administered short time interval, minimum toxic concentration of drug may be reached, with toxic side effect can occur. If doses are missed or forgetted, the administered drug goes to sub therapeutic levels on those below the minimum effective concentration (MEC) may result, so there is no use to the patient.

**1.3.4. Designing sustained-release drug delivery system:** *(Shalin A. Modi, et al., 2011)*

Most of the orally administered drugs, targeting is not a primary concern and it is usually intended for drugs to penetrate to the general circulation and perfuse to other body tissues. For this reason, most systems employed are of the sustained release variety. It is assumed that increasing concentration at the absorption site will increase circulating blood levels, which in turn, promotes greater concentration of drug at the site of action. If toxicity is not an issue, therapeutic levels can thus be extended. In essence, drug delivery by these systems usually depends on release from some type of dosage form, permeation through biological milieu and absorption through an epithelial membrane to the blood. There are a variety of both physicochemical and biological factors that come into play in the design of such system.

**1.3.5. Factors Affecting Sustained Release Dosage Forms:** (*Chein Y.W., 2009; http://www.pharmainfo.net)*

**1.3.5.1. Physicochemical properties of drug:**

**a) Dose Size:**

If an oral product has a dose size greater that 0.5gm it is a poor candidate for sustained release system, Since addition of sustaining dose and possibly the sustaining mechanism will, in most cases generates a substantial volume product that unacceptably large.

**b) Aqueous Solubility:**

Most of drugs are weak acids or bases, since the unchanged form of a drug preferentially permeates across lipid membranes drugs aqueous solubility will generally be decreased by conversion to an unchanged form for drugs with low water solubility will be difficult to incorporate into sustained release mechanism. The lower limit on solubility for such product has been reported 0.1mg/ml. drugs with great water solubility are equally difficult to incorporate in to sustained release system. pH dependent solubility, particularly in the physiological pH range, would be another problem because of the variation in pH throughout the GI tract and hence variation in dissolution rate.

**c) Partition Coefficient:**

Partition coefficient is generally defined as the fraction of drug in an oil phase to that of an adjacent aqueous phase. Accordingly compounds with relatively high partition coefficient are predominantly lipid soluble and consequently have very law aqueous solubility. Compounds with very law partition coefficients will have difficulty in penetrating membranes resulting poor bioavailability.

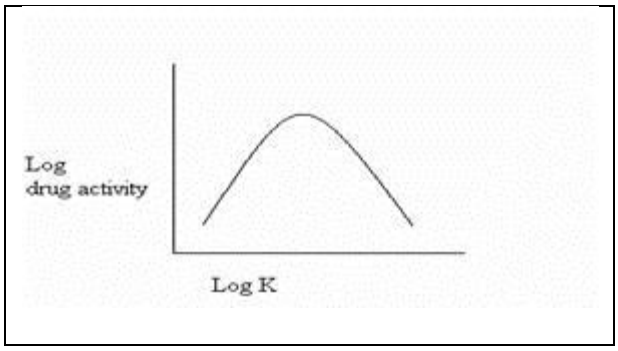



**Figure 1.2:** Typical relationship between drug activity and partition coefficient K.

**d) Dissociation constant (pka):**

The relationship between dissociation constant of compound and absorptive environment. Presenting drug in an unchanged form is adventitious for drug permeation but solubility decrease as the drug is in unchanged form.

**e) Drug Stability:**

Orally administered drugs can be subject to both acid base hydrolysis and enzymatic degradation. Degradation will proceed at the reduced rate for drugs in the solid state, for drugs that are unstable in stomach, systems that prolong delivery ever the entire course of transit in GI tract are beneficial. Compounds that are unstable in the small intestine may demonstrate decreased bioavailability when administered form a sustaining dosage from. This is because more drug is delivered in small intestine and hence subject to degradation.

**f) Molecular size and diffusivity:**

The ability of drug to diffuse through membrane it's so called diffusivity & diffusion coefficient is function of molecular size (or molecular weight). Generally, values of diffusion coefficient for intermediate molecular weight drugs, through flexible polymer range from 10-8 to 10-9 $cm^2$ / sec. with values on the order of 10-8 being most common for drugs with molecular weight greater than 500, the diffusion

coefficient in many polymers frequently are so small that they are difficult to quantify i.e. less than 16-12 $cm^2$/sec. Thus high molecular weight drugs and / or polymeric drugs should be expected to display very slow release kinetics in sustained release device using diffusion through polymer membrane.

**g) Protein binding:**

It is well known that many drugs bind to plasma proteins with a concomitant influence on the duration of drug action. Since blood proteins are for the most part re-circulated and not eliminated, drug Protein binding can serve as a depot for drug producing a prolonged release profile, especially if a high degree of drug binding occurs.

Extensive binding to plasma proteins will be evidenced by a long half life of elimination for drugs and such drugs generally most require a sustained release dosage form. However drugs that exhibit high degree of binding to plasma proteins also might bind to bio-polymers in GI tract which could have influence on sustained drug delivery. The presence of hydrophobic moiety on drug molecule also increases the binding potential.

**1.3.5.2. Biological factors:**

**a) Biological Half Life:**

The usual goal of an oral sustained release product is to maintain therapeutic blood levels over an extended period. To action this, drug must enter in the circulation of approximately the same rate of which it is eliminated. The elimination rate is quantitatively described by half-life ($t_{1/2}$). Therapeutic compounds with short half lives are excellent candidates for sustained release preparations. Since this can reduce dosing frequency. In general drugs with half-lives shorter than 3hrs are poor candidates of sustained release dosage forms of dose size will increase as well as

compounds with long half lives, more than 8 hrs are also not used in sustained release forms because their effect is already sustained.

**b) Absorption:**

The rate, extent and uniformity of absorption of a drug are important factors when considered its formulation into a sustained release system. As the rate limiting step in drug delivery from a sustained-release system is its release from a dosage form, rather than absorption. Rapid rate of absorption of drug, relative to its release is essential if the system is to be successful. It we assume that transit time of drug must in the absorptive areas of the GI tract is about 8-12 hrs. The maximum half life for absorption should be approximately 3-4 hrs. Otherwise device will pass out of potential absorption regions before drug release is complete.

**c) Distribution:**

The distribution of drugs into tissues can be important factor in the overall drug elimination kinetics. Since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibrium with blood and extra vascular tissue, consequently apparent volume of distribution assumes different values depending on time course of drug disposition. For design of sustained/ controlled release products, one must have information of disposition of drug.

**d) Metabolism:**

Drugs that are significantly metabolized before absorption, either in lumen or the tissue of the intestine, can show decreased bioavailability from slower-releasing dosage forms. Most intestinal wall enzymes systems are saturable. As drug is released at a slower rate to these regions less total drug is presented to the enzymatic. Process device a specific period, allowing more complete conversion of the drug to its metabolite.

**e) Side effects:**

The incidence of side effect of a drug is depends on its therapeutic concentration level in blood. It can be remedy by the drug concentration level is controlled at which timing that drug exists in blood after administration. Toxic effect of a drug is expected above the maximum effective range level and fall in the therapeutic effect if a drug below the level of minimum effective range. So the above problem we can solve by making sustained release preparation.

**f) Margin of safety:**

Therapeutic index of a drug is very important for either sustained or controlled release delivery system. Its value only desired the margin of safety. Therapeutic index value it has been longer means excellent for preparation of sustained release tablet. Narrow therapeutic index of some drug precise to release the active content in therapeutic safe and effective range. Some drug like cardiac glycosides that therapeutic index value is very small, so it's not used for sustained release delivery system.

Therapeutic index = $TD_{50}/ED_{50}$

Where, $TD_{50}$ - Median toxic dose

$ED_{50}$ - Median effective dose.

**1.4. Oral controlled and sustained release systems:** (*Chein Y.W., 2009; http://www.pharmainfo.net; Shalin A. Modi, et al., 2011)*

The controlled release systems for oral use are mostly solids and based on dissolution, diffusion or a combination of both mechanisms in the control of release rate of drug. Depending upon the manner of drug release, these systems are classified as follows:

### 1.4.1. Continuous release systems:

These systems release the drug for a prolonged period of time along the entire length of gastrointestinal tract with normal transit of the dosage form. The various systems under this category are as follow,

A. Dissolution controlled release systems

B. Diffusion controlled release systems

C. Dissolution and diffusion controlled release systems

D. Ion exchange resin- drug complexes

E. pH dependent formulation

F. Osmotic pressure controlled systems

### A. Dissolution controlled release systems:

These types of systems are easiest to design. The drug present in such system may be the one:

- With inherently slow dissolution rate e.g. Griseofulvin and Digoxin.
- That produces slow dissolving forms, when it comes in contact with GI fluids.
- Having high aqueous solubility and dissolution rate.

Drugs having high aqueous solubility and dissolution rate, shows challenge in controlling their dissolution rate. Dissolution-controlled release can be obtained by slowing the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer and coating drug particles or granules with polymeric materials of varying thickness. The rate limiting step for dissolution of a drug is the diffusion across the aqueous boundary layer. The solubility of the drug provides the source of energy for drug release, which is countered by the stagnant-fluid diffusional boundary layer. The rate of dissolution (dm/dt) can be approximated by below equation.

$$Dm/dt = ADS/h$$

Where, S = Aqueous solubility of the drug.

A = Surface area of the dissolving particle or tablet.

D = Diffusivity of the drug and

h = Thickness of the boundary layer.

**a) Matrix (or monolithic) dissolution controlled systems:**

As the drug is homogeneously dispersed throughout the rate controlling medium, this system is also called as monolith system. It is very common and employs waxes such as bees wax, carnauba wax which control the drug release rate by controlling the rate of dissolution fluid penetration into the matrix by altering the porosity of tablet, decreasing its wettability or by itself getting dissolved at a slower rate. The drug release is often first order from such matrices.

**b) Reservoir (Encapsulation) dissolution controlled systems:**

In this type, the drug particles are coated or encapsulated by one of the several microencapsulation techniques with slowly dissolving materials like cellulose and polyethylene glycol. The dissolution rate of coat depends upon the solubility and thickness of the coating.

**B. Diffusion controlled systems:**

The basic mechanism of drug release from these two systems is fundamentally different besides these simple systems, combination of reservoir and monolithic systems also exist in practice.Diffusion systems are characterized by release rate of drug is dependent on its diffusion through inert water insoluble membrane barrier.

There are basically two types of diffusion devices.

a) Reservoir devices

b) Matrix devices

**a) Reservoir Devices:**

Reservoir Devices are those in which a core of drug is surrounded by polymeric membrane. The nature of membrane determines the rate of release of drug from system. The process of diffusion is generally described by a series of equations governed by Fick's first law of diffusion.

$$J = -D (DC/ DX)\ldots\ldots (1)$$

Where, 'J' is the flux of drug across the membrane given in units of amount / area time.

'D' is diffusion coefficient of drug in membrane in units of area / time. This is reflecting to drug molecule's ability to diffuse through the solvent and is dependent on the factors as molecular size and charge.

'dc/dt' represents rate of change in concentration C relative to a distance X in the membrane.

The law states that amount of drug passing across a unit area, is proportional to the concentration difference across that plane.

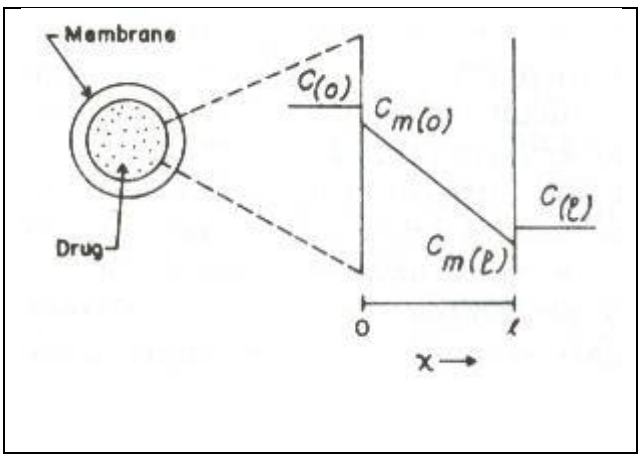



**Figure 1.3:** Schematic representation of reservoir diffusion device Cm (o), and Cm (d) represent concentration of drug inside surfaces of membrane and C (o) & C(d) represents concentration in adjacent regions.

If it is assumed that the drug on the both side of membrane is in equilibrium with its respective membrane surface which in equilibrium between the membrane surfaces and their bathing solutions as shown in Figure. Therefore the concentration just inside the membrane surface can be related to the concentration in the adjacent region by following expression.

$$K = Cm(o) / C(d) \quad \text{at } X = o \qquad (2)$$

$$K = Cm(d) / C(d) \quad \text{at } X = d \qquad (3)$$

Where K = partition coefficient.

If we consider K & D are constants then equation (1) becomes,

$$J = D K \Delta C/d \qquad (4)$$

Where $\Delta c$ is the concentration difference across the membrane and d is path length of diffusion. The simplest system to consider is that of slab, where drug release is from only one surface as shown Figure in this case equation (4) becomes

$$dMt/ dt = ADK \Delta C/ d \qquad (5)$$

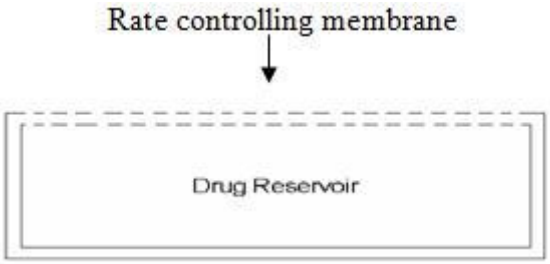



**Figure 1.4:** Diagrammatic representation of slab configuration of reservoir diffusion system.

Where Mt = Mass of drug released after time t, dMt/dt. Steady state drug release rate of time't'; A= surface area of device.

In equation (7) if variables of right side of equation remain constant, then left side of equation represents release rate of system, a true controlled release system with a zero-order release rate.

A constant effective area of diffusion, diffusional path length, concentration difference, and diffusion coefficient are required to obtain a release rate that is constant. Reservoir diffusional systems have several advantages over conventional dosage forms. They can after zero order release of drug, kinetics of which can be controlled by changing the characteristics of the polymer to meet the particular drug and therapy conditions.

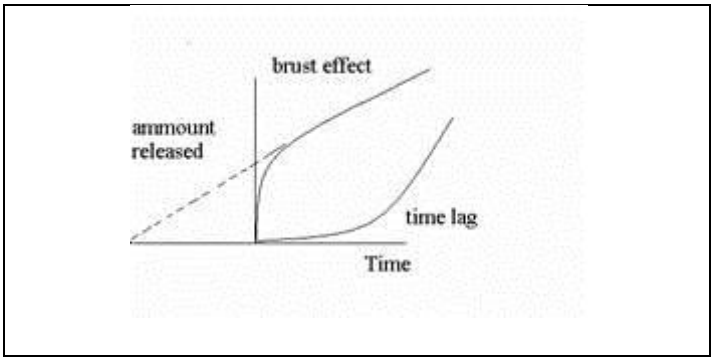



**Figure 1.5:** Plot showing approach to steady state for reservoir device that has been stored for an extended period (the burst effect curve) and for device that has been freshly made (the time lag curve).

Common methods used to develop reservoir type of devices include micro encapsulation of drug particles and press coating of tablets containing drug cores. In most cases particles coated by microencapsulation form a system where the drug is contained in the coating film as well as in the core of micro capsule. The drug release generally involves combination of dissolution and diffusion with dissolution being process that controls the release rate. If encapsulating material is selected properly will be the controlling process. Some materials such as membrane barrier coat alone

or in combination, are hardened gelatin, methyl or methylcellulose, polyhydroxy methacrylate hydroxypropyl methylcellulose, polydroxy methacrylate, polyvinyl acetate & various waxes.

**Matrix devices:**

A matrix device, as the name implies, consists of drug dispersed homogenously throughout a polymer.

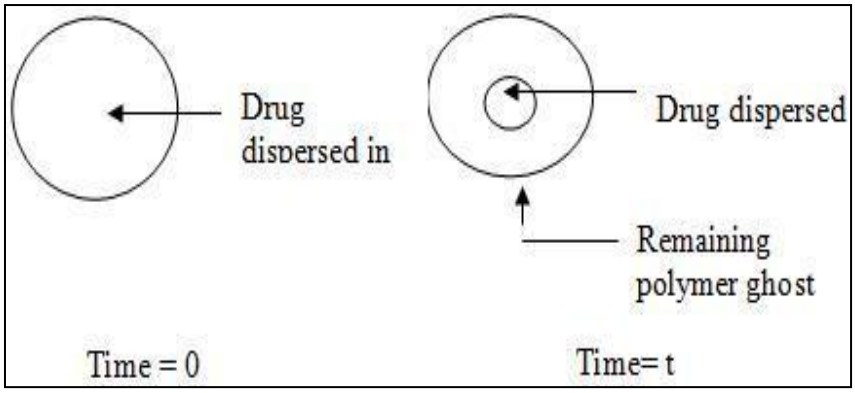



**Figure 1.6:** Matrix diffusion system before release (time=0) & after partial drug Release (time=t).

In this model drug in outside layer exposed to the bathing solution is dissolved first and diffused out of the matrix. This process continues with the interface between bathing solution and the solid drug moving controlled, the rate of dissolution of drug particles within the matrix must be faster that the diffusion rate of dissolved drug leaving matrix.

Following assumptions are made in retrieving the mathematical models are:

i. A pseudo steady state is maintained during drug release.

ii. The diameter of drug particles is less than the average distance of drug Diffusion through the matrix.

iii. The bathing solution provides sink conditions.

iv. The diffusion coefficient of drug in the matrix remains constant.

The next equation that describes the rate of release drugs dispersed in an inert matrix system has been derived by Higuchi.

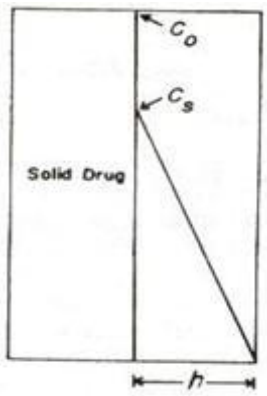



**Figure 1.7:** Schematic representation of the physical model used for a planer slab matrix diffusion device.

The change in amount of drug released per unit area dM and change in the thickness of the zone of the matrix that has been depleted of the drug,

$$dM/dh = Co\ dh - Cs\ /2 \qquad (6)$$

By Fick's first law,

$$dm = (Dm\ Cs/h)\ dt. \qquad (7)$$

where, Dm is diffusion coefficient in matrix if equation (6) & (7) are equated & solved for D that value of h sustituted back into the integrated form of equation (7) An equation for M is obtained.

$$M = [Cs\ Dm\ (2Co - Cs)\ t]\ ½ \qquad (8)$$

Similarly, a drug released from porous or granular matrix is described.

$$M = [Ds\ Ca\ (\epsilon/\tau)\ (2Co - \epsilon\ Ca)\ t]\ ½ \qquad (9)$$

Where, e = Porosity of matrix

$\tau$ = tortuosity.

Ca = Solubility of drug in release medium

Ds = diffusion coefficient of drug in release medium.

In this system drug is leached from matrix through channels or pores.

$$M = Kt^{1/2}$$

$$M = K\sqrt{t} \qquad (10)$$

Where K is constantan so, that plot amount of drug released verses square root of time should be linear if the release of drug from the matrix is diffusion controlled. The release rate of drug from such a device is not zero order, since if decreases with time but as previously mentioned, this may be clinically equivalent to constant drugs.

**1.5. Matrix tablets:** (*Chein Y.W., 2009; Harnish Patel, et al., 2011)*

Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating SR dosage form.

Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems.

Matrix systems are widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or

dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients.

Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs.

**1.5.1. Advantages of matrix tablets:**

- Easy to manufacture
- Versatile, effective and low cost
- Can be made to release high molecular weight compounds
- The sustained release formulations may maintain therapeutic concentrations over prolonged periods.
- The use of sustain release formulations avoids the high blood concentration.
- Sustain release formulations have the potential to improve the patient compliance.
- Reduce the toxicity by slowing drug absorption.
- Increase the stability by protecting the drug from hydrolysis or other derivative changes in gastrointestinal tract.
- Minimize the local and systemic side effects.
- Improvement in treatment efficacy.
- Minimize drug accumulation with chronic dosing.

- Usage of less total drug.
- Improvement the bioavailability of some drugs.
- Improvement of the ability to provide special effects.

  Ex: Morning relief of arthritis through bed time dosing.

**1.5.2. Disadvantages of matrix tablet:**

- The remaining matrix must be removed after the drug has been released.
- High cost of preparation.
- The release rates are affected by various factors such as, food and the rate transit through the gut.
- The drug release rates vary with the square root of time. Release rate continuously diminishes due to an increase in diffusional resistance and/or a decrease in effective area at the diffusion front. However, a substantial sustained effect can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order.

**1.5.3. Classification of matrix tablets:**

**1.5.3.1. On the Basis of Retardant Material Used:**

Matrix tablets can be divided into 5 types.

**1. Hydrophobic Matrices (Plastic matrices):**

The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. In this method of obtaining sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in to a tablet.

Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles. Examples of materials that have been used as inert or hydrophobic matrices

include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers. The rate-controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid.

**2. Lipid Matrices:**

These matrices prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation.

**3. Hydrophilic Matrices:**

Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. The formulation of the drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients is of particular interest in the field of controlled release. Infect a matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swellable controlled release systems.

The polymers used in the preparation of hydrophilic matrices are divided into three broad groups,

**A. Cellulose derivatives:**

Methylcellulose 400 and 4000Cps, Hydroxy ethylcellulose; Hydroxypropyl methylcellulose (HPMC) 25, 100, 4000 and 15000Cps; and Sodium carboxy methyl cellulose.

**B. Non cellulose natural or semi synthetic polymers:**

Agar-Agar; Carob gum; Alginates; Molasses; Polysaccharides of mannose and galactose, Chitosan and Modified starches.

**Polymers of acrylic acid:**

Carbopol-934, the most used variety.

**4. Biodegradable Matrices:**

These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. They are biologically degraded or eroded by enzymes generated by surrounding living cells or by non-enzymatic process in to oligomers and monomers that can be metabolized or excreted. Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

**5. Mineral Matrices:**

These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaephyceae) by the use of dilute alkali.

**1.5.3.2. On the Basis of Porosity of Matrix:**

Matrix system can also be classified according to their porosity and consequently, Macro porous; Micro porous and Non-porous systems can be identified:

**1. Macro porous Systems:**

In such systems the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 μm. This pore size is larger than diffusant molecule size.

**2. Micro porous System:**

Diffusion in this type of system occurs essentially through pores. For micro porous systems, pore size ranges between 50 – 200 A°, which is slightly larger than diffusant molecules size.

**3. Non-porous System:**

Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.

**1.5.4. Polymers used in matrix tablet:**

**Hydrogels:**

Polyhydroxy ethyl methacrylate (PHEMA), Cross-linked polyvinyl alcohol (PVA), Cross-linked polyvinyl pyrrolidone (PVP), Polyethylene oxide (PEO), Poly acrylamide (PA).

**Soluble polymers:**

Polyethyleneglycol (PEG), polyvinyl alcohol (PVA), Polyvinyl pyrrolidone (PVP), Hydroxypropyl methyl cellulose (HPMC).

**Biodegradable polymers:**

Polylactic acid (PLA), Polyglycolic acid (PGA), Poly caprolactone (PCL), Poly anhydrides, Poly orthoesters.

**Non-biodegradable polymers:**

Polyethylene vinyl acetate (PVA), Poly dimethyl siloxane (PDS), Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC).

**Mucoadhesive polymers:**

Poly carbophil, Sodium carboxy methylcellulose, Polyacrylic acid, Tragacanth, Methyl cellulose, Pectin.

**Natural gums:** Xanthan gum, Guar gum, Karaya gum, Locust bean gum.

**1.5.5. Mechanism of drug release from matrix tablet:**

Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix. Derivation of the mathematical model to describe this system involves the following assumptions:

a) A pseudo-steady state is maintained during drug release,

b) The diameter of the drug particles is less than the average distance of drug diffusion through the matrix,

c) The bathing solution provides sink conditions at all times.

**1.6. Methods used in tablet manufacturing:** *(Lieberman H.A. and Lachman L., 1999; Ansel H.C., 2009; http://www.pharmainfo.net)*

**Granulation:**

Granulation may be defined as a size enlargement process which converts small particles into physically stronger & larger agglomerates.

**The reason for granulation:**

- Become the pharmaceutical ingredient are free flowing
- Increase the denseness of ingredient
- We can formulate uniform granular size that does not existing apart
- Produce better compression characteristic of drug
- Controlling the rate of drug release from the dosage form
- Reduce dust in granulation technique
- The appearance of tablet can be achieved

**Methods:**

1. Direct compression
2. Wet granulation
3. Dry granulation

**1.6.1. Direct compression:**

In early days, most of the tablets require granulation of the powdered Active Pharmaceutical Ingredient (API) and Excipients. At the availability of new excipients or modified form of old excipients and the invention of new tablet machinery or modification of old tablet machinery provides an ease in manufacturing of tablets by simple procedure of direct compression.

Amongst the techniques used to prepare tablets, direct compression is the most advanced technology. It involves only blending and compression. Thus offering

advantage particularly in terms of speedy production. Because it requires fewer unit operations, less machinery, reduced number of personnel and considerably less processing time along with increased product stability.

**1.6.1.1. Definition:**

The term "direct compression" is defined as the process by which tablets are compressed directly from powder mixture of API and suitable excipients. No pretreatment of the powder blend by wet or dry granulation procedure is required.

**1.6.1.2. The events that motivates the industry people to use direct compression technique:**

I. Commercial availability of the directly compressible excipients possessing both good compressibility and good flowability. For example, Spray dried lactose, Anhydrous lactose, Starch-1500, microcrystalline cellulose, Di-Pac$^{Ò}$, sorbitol.

II. Major advances in tablet compression machinery:

i) Improved positive die feeding,

ii) Precompression of powder blend.

**1.6.1.3 Merits:**

i) Direct compression is more efficient and economical process as compared to other processes, because it involves only dry blending and compaction of API and necessary excipients.

ii) The most important advantage of direct compression is economical process. Reduced processing time, reduced labor costs, fewer manufacturing steps, and less number of equipments are required, less process validation, reduced consumption of power.

iii) Elimination of heat and moisture, thus increasing not only the stability but also the suitability of the process for thermolabile and moisture sensitive API's.

iv) Particle size uniformity.

v) Prime particle dissolution.

In case of directly compressed tablets after disintegration, each primary drug particle is liberated. While in the case of tablets prepared by compression of granules, small drug particles with a larger surface area adhere together into larger agglomerates; thus decreasing the surface area available for dissolution.

vi) The chances of batch-to-batch variation are negligible, because the unit operations required for manufacturing processes is fewer.

vii) Chemical stability problems for API and excipient would be avoided.

viii) Provides stability against the effect of aging which affects the dissolution rates.

**1.6.1.4. Merits over wet granulation process:**

The variables faced in the processing of the granules can lead to significant tableting problems. Properties of granules formed can be affected by viscosity of granulating solution, the rate of addition of granulating solution, type of mixer used and duration of mixing, method and rate of dry and wet blending. The above variables can change the density and the particle size of the resulting granules and may have a major influence on fill weight and compaction qualities. Drying can lead to unblending as soluble API migrates to the surface of the drying granules.

**1.6.1.5. Demerits:**

**Excipients Related:**

i) Problems in the uniform distribution of low dose drugs.

ii) High dose drugs having high bulk volume, poor compressibility and poor flowability are not suitable for direct compression.

iii) The choice of excipients for direct compression is extremely critical. Direct compression diluents and binders must possess both good compressibility and good flow ability.

iv) Many active ingredients are not compressible either in crystalline or amorphous forms.

v) Direct compression blends may lead to unblending because of difference in particle size or density of drug and excipients. Similarly the lack of moisture may give rise to static charges, which may lead to unblending.

vi) Non-uniform distribution of colour, especially in tablets of deep colours.

**Process Related:**

i) Capping, lamination, splitting, or layering of tablets is sometimes related to air entrapment during direct compression. When air is trapped, the resulting tablets expand when the pressure of tablet is released, resulting in splits or layers in the tablet.

ii) In some cases require greater sophistication in blending and compression equipments.

iii) Direct compression equipments are expensive.

**1.6.1.6. Manufacturing steps for direct compression:**

Direct compression involves comparatively few steps:

- Milling of drug and excipients.
- Mixing of drug and excipients.
- Tablet compression.

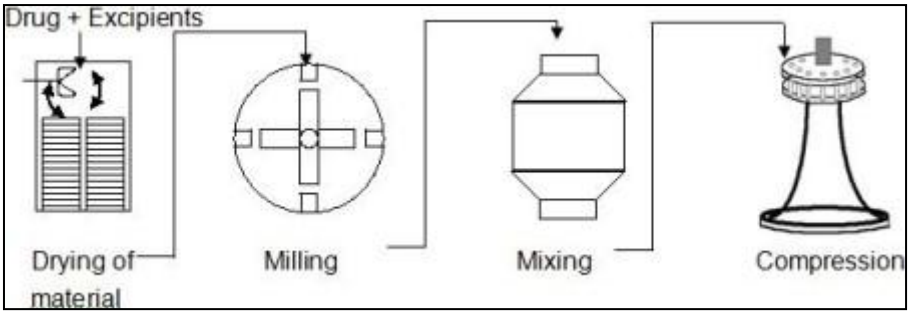



**Figure 1.8:** Manufacturing Steps for Direct Compression.

**1.6.1.7. Direct compression Excipients:**

Direct compression excipients mainly include diluents, binders and disintegrants. Generally these are common materials that have been modified during the chemical manufacturing process, in such a way to improve compressibility and flowability of the material.

The physicochemical properties of the ingredients such as particle size, flowability and moisture are critical in direct compression tableting. The success of direct compression formulation is highly dependent on functional behavior of excipients.

**1.6.1.7.1. An ideal direct compression excipient should possess the following attributes:**

i) It should have good compressibility.

ii) It should possess good hardness after compression, that is material should not possess any deformational properties; otherwise this may lead to capping and lamination of tablets.

iii) It should have good flowability.

iv) It should be physiologically inert.

v) It should be compatible with wide range of API.

vi) It should be stable to various environmental conditions (air, moisture, heat, etc.).

vii) It should not show any physical or chemical change in its properties on aging.

viii) It should have high dilution potential i.e. able to incorporate high amount of API.

ix) It should be colourless, odorless and tasteless.

x) It should accept colourants uniformity.

xi) It should possess suitable organoleptic properties according to formulation type, that is in case of chewable tablet diluent should have suitable taste and flavor. For example, mannitol produces cooling sensation in mouth and also sweet test.

xii) It should not interfere with bioavailability and biological activity of active ingredients.

xiii) It should be easily available and economical in cost.

**Granulation method can be broadly classified into two types:**

- Wet granulation and
- Dry granulation.

**1.6.2. Wet granulation:**

The most widely used process of agglomeration in pharmaceutical industry is wet granulation. Wet granulation process simply involves wet massing of the powder blend with a granulating liquid, wet sizing and drying.

**1.6.2.1. Important steps involved in the wet granulation:**

i) Mixing of the drug(s) and excipients

ii) Preparation of binder solution

iii) Mixing of binder solution with powder mixture to form wet mass.

iv) Coarse screening of wet mass using a suitable sieve (6-12 # screens).

v) Drying of moist granules.

vi) Screening of dry granules through a suitable sieve (14-20 # screen).

vii) Mixing of screened granules with disintegrant, glidant, and lubricant.

**1.6.2.2. Limitations of wet granulation:**

i) The greatest disadvantage of wet granulation is its cost. It is an expensive process because of labor, time, equipment, energy and space requirements.

ii) Loss of material during various stages of processing

iii) Stability may be major concern for moisture sensitive or thermo labile drugs

iv) Multiple processing steps add complexity and make validation and control difficult.

v) An inherent limitation of wet granulation is that any incompatibility between formulation components is aggravated.

**1.6.3. Dry granulation:**

In dry granulation process the powder mixture is compressed without the use of heat and solvent. It is the least desirable of all methods of granulation. The two basic procedures are to form a compact of material by compression and then to mill the compact to obtain a granules. Two methods are used for dry granulation. The more widely used method is slugging, where the powder is pre-compressed and the resulting tablet or slug are milled to yield the granules.

The other method is to pre-compress the powder with pressure rolls using a machine such as Chilosonator.

**1.6.3.1. Advantages:**

The main advantages of dry granulation or slugging are that it uses less equipments and space. It eliminates the need for binder solution, heavy mixing equipment and the costly and time consuming drying step required for wet granulation. Slugging can be used for advantages in the following situations:

i) For moisture sensitive material

ii) For heat sensitive material

iii) For improved disintegration since powder particles are not bonded together by a binder

**1.6.3.2. Disadvantages:**

i) It requires a specialized heavy duty tablet press to form slug

ii) It does not permit uniform colour distribution

iii) Achieved with wet granulation where the dye can be incorporated into binder liquid.

iv) The process tends to create more dust than wet granulation, increasing the potential contamination.

**1.7. AIDS and HIV review:** *(http://www.emedicinehealth.com; http://www.biog1105-1106.org)*

HIV (Human Immunodeficiency Virus) infection has now spread to every country in the world. Approximately 40 million people are currently living with HIV infection, and an estimated 25 million have died from this disease. The scourge of HIV has been particularly devastating in sub-Saharan Africa, but infection rates in other countries remain high. In the United States, approximately 1 million people are currently infected. Here are a few key points about the disease:

- Globally, 85% of HIV transmission is heterosexual.
- In the United States, approximately one-third of new diagnoses appear to be related to heterosexual transmission. Male-to-male sexual contact still accounts for approximately half of new diagnoses in the U.S. Intravenous drug use contributes to the remaining cases. Because the diagnosis may occur years after infection, it is likely that a higher proportion of recent infections are due to heterosexual transmission.

- Infections in women are increasing. Worldwide, 42% of people with HIV are women. In the United States, approximately 25% of new diagnoses are in women, and the proportion is rising.
- There is good news on one front. New HIV infections in U.S. children have fallen dramatically. This is largely a result of testing and treating infected mothers, as well as establishing uniform testing guidelines for blood products.

**In order to understand HIV and AIDS, it is important to understand the meanings behind these terms:**

- HIV stands for the human immunodeficiency virus. It is one of a group of viruses known as retroviruses. After getting into the body, the virus kills or damages cells of the body's immune system. The body tries to keep up by making new cells or trying to contain the virus, but eventually the HIV wins out and progressively destroys the body's ability to fight infections and certain cancers.
- AIDS stands for the acquired immunodeficiency syndrome. It is caused by HIV and occurs when the virus has destroyed so much of the body's defenses that immune-cell counts fall to critical levels or certain life-threatening infections or cancers develop.

### 1.7.1. HIV/AIDS Transmission:

HIV is transmitted when the virus enters the body, usually by injecting infected cells or semen. There are several possible ways in which the virus can enter.

- Most commonly, HIV infection is spread by having sex with an infected partner. The virus can enter the body through the lining of the vagina, vulva, penis, rectum, or mouth during sex.

- HIV frequently spreads among injection-drug users who share needles or syringes that are contaminated with blood from an infected person.
- Women can transmit HIV to their babies during pregnancy or birth, when infected maternal cells enter the baby's circulation.
- HIV can be spread in health-care settings through accidental needle sticks or contact with contaminated fluids.
- Very rarely, HIV spreads through transfusion of contaminated blood or blood components. Blood products are now tested to minimize this risk. If tissues or organs from an infected person are transplanted, the recipient may acquire HIV. Donors are now tested for HIV to minimize this risk.
- People who already have a sexually transmitted disease, such as syphilis, genital herpes, chlamydial infection, gonorrhea, or bacterial vaginosis, are more likely to acquire HIV infection during sex with an infected partner.

The virus does not spread through casual contact such as preparing food, sharing towels and bedding, or via swimming pools, telephones, or toilet seats. The virus is also unlikely to be spread by contact with saliva, unless it is contaminated with blood.

**1.7.2. Structure of HIV:**

The two copies of the viral RNA are protected by a protein coat and enclosed in a capsule. Also contained in the capsule are reverse transcriptase enzymes (which convert the single-stranded RNAs into double-stranded DNA copies), integrase (which inserts the DNA version into the host genome), and protease (which cuts the long chain of polypeptides produced by viral RNA into individual enzyme components as new virus particles are budding off a cell membrane). The capsule is itself enclosed in a bilayer membrane obtained from the previous host cell; in the membrane are mounted P17 (the remains of a protein involved in budding off) and

GP120 (the glycoprotein that binds the helper T-cell receptor and so enables the virus to gain entry into its host).

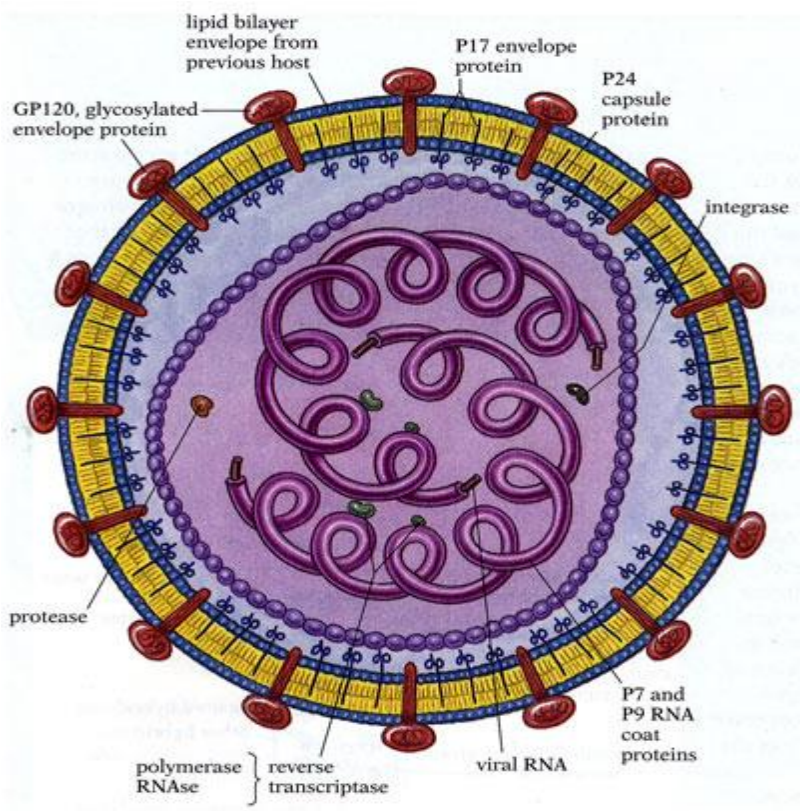



**Figure 1.9:** Structure of HIV.

### 1.7.3. HIV/AIDS Symptoms and Signs:

Many people with HIV do not know they are infected.

- Many people do not develop symptoms after they first get infected with HIV. Others have a flu-like illness within several days to weeks after exposure to the virus. They complain of fever, headache, tiredness, and enlarged lymph nodes in the neck. These symptoms usually disappear on their own within a few weeks. After that, the person feels normal and has no symptoms. This asymptomatic phase often lasts for years.
- The progression of disease varies widely among individuals. This state may last from a few months to more than 10 years.

- During this period, the virus continues to multiply actively and infects and kills the cells of the immune system.
- The virus destroys the cells that are the primary infection fighters, a type of white blood cell called CD4 cells.
- Even though the person has no symptoms, he or she is contagious and can pass HIV to others through the routes listed above.

AIDS is the later stage of HIV infection, when the body begins losing its ability to fight infections. Once the CD4 cell count falls low enough, an infected person is said to have AIDS. Sometimes, the diagnosis of AIDS is made because the person has unusual infections or cancers that show the weak immune system.

- The infections that happen with AIDS are called opportunistic infections because they take advantage of the opportunity to infect a weakened host. The infections include (but are not limited to)
  - Pneumonia caused by *Pneumocystis*, which causes wheezing;
  - Brain infection with toxoplasmosis which can cause trouble thinking or symptoms that mimic a stroke;
  - Widespread infection with a bacteria called MAC (mycobacterium avium complex) which can cause fever and weight loss;
  - Yeast infection of the swallowing tube (esophagus) which causes pain with swallowing;
  - Widespread diseases with certain fungi like histoplasmosis, which can cause fever, cough, anemia, and other problems.
- A weakened immune system can also lead to other unusual conditions:
  - Lymphoma in (a form of cancer of the lymphoid tissue) the brain, which can cause fever and trouble thinking;

- A cancer of the soft tissues called Kaposi's sarcoma, which causes brown, reddish, or purple spots that develop on the skin or in the mouth.

**1.7.4. HIV/AIDS Diagnosis:**

HIV infection is commonly diagnosed by blood tests. There are three main types of tests that are commonly used: (1) antibody tests, (2) RNA tests, and (3) a combination test that detects both antibodies and a piece of the virus called the p24 protein. In addition, a blood test known as a Western blot is used to confirm the diagnosis.

Testing for HIV is usually a two-step process. First, an inexpensive screening test is done. If that test is positive, a second test (Western blot) is done to confirm the result. Antibody tests are the most common initial screening test used. There are different types of antibody screening tests available:

- Most commonly, blood is drawn for an enzyme immunoassay (EIA). The test is usually run in a local laboratory, so results can take one to three days to come back.
- Other tests can detect antibodies in body fluids other than blood such as saliva, urine, and vaginal secretions. Some of these are designed to be rapid tests that produce results in approximately 20 minutes. These tests have accuracy rates similar to traditional blood tests.
- HIV home-testing kits are available at many local drug stores. Blood is obtained by a finger prick and blotted on a filter strip. Other test kits use saliva or urine. The filter strip is mailed in a protective envelope to a laboratory to be tested. Results are returned by mail in one to two weeks.

- All positive antibody screening tests must be confirmed with a follow-up blood test called the Western blot to make a positive diagnosis. If the antibody test and the Western blot are both positive, the likelihood of a person being HIV infected is >99%. Sometimes, the Western blot is "indeterminate," meaning that it is neither positive nor negative. In these cases, the tests are usually repeated at a later date. In addition, an RNA test for the virus might be done.

Other tests, such as those that look for virus RNA and the combination tests are not commonly used for screening.

**1.7.5. HIV/AIDS Treatment:**

**Medications:**

The following are the different classes of medications used in treatment.

- **Reverse transcriptase inhibitors:** These drugs inhibit the ability of the virus to make copies of itself. The following are examples:
    - Nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs). These include medications such as zidovudine (AZT/Retrovir), didanosine (ddI/Videx), zalcitabine (ddC/Hivid), stavudine (d4T/Zerit), lamivudine (3TC/Epivir), abacavir (ABC/Ziagen), emtricitabine (FTC/Emtriva), and tenofovir (Viread).
    - Non-nucleoside reverse transcriptase inhibitors (NNRTIS) are commonly used in combination with NRTIs to help keep the virus from multiplying. Examples of NNRTIs are efavirenz (Sustiva), nevirapine (Viramune), and delavirdine (Rescriptor). Etravirine (Intelence), a newer member of this class of drugs, was approved by the U.S. FDA in 2008.

- **Protease inhibitors (PIs):**

  These medications interrupt virus replication at a later step in its life cycle, preventing cells from producing new viruses. These include ritonavir (Norvir), a lopinavir and ritonavir combination (Kaletra), saquinavir (Invirase), indinavir sulphate (Crixivan), amprenavir (Agenerase), fosamprenavir (Lexiva), darunavir (Prezista), atazanavir (Reyataz), tipranavir (Aptivus), and nelfinavir (Viracept). Using PIs with NRTIs reduces the chances that the virus will become resistant to medications.

- Fusion and entry inhibitors are newer agents that keep HIV from entering human cells. Enfuvirtide (Fuzeon/T20) was the first drug in this group. It is given in injectable form like insulin. Another drug called maraviroc (Selzentry) binds to a protein on the surface of the human cell and can be given by mouth. Both drugs are used in combination with other anti-HIV drugs.

- Integrase inhibitors stop HIV genes from becoming incorporated into the human cell's DNA. This is a newer class of drugs recently approved to help treat those who have developed resistance to the other medications. Raltegravir (Isentress) was the first drug in this class approved by the FDA in 2007.

Anti-retroviral drugs stop viral replication and delay the development of AIDS. However, they also have side effects that can be severe. They include decreased levels of red or white blood cells, inflammation of the pancreas, liver toxicity, rash, gastrointestinal problems, elevated cholesterol level, diabetes, abnormal body-fat distribution, and painful nerve damage.

- Pregnant women who are HIV-positive should seek care immediately because HAART therapy reduces the risk of transmitting the virus to the fetus. There are certain drugs, however, that are harmful to the baby. Therefore, seeing a physician to discuss anti-HIV medications is crucial.

# NEED AND OBJECTIVES

# 2. NEED AND OBJECTIVES

**Need of this work are:**

- Lamivudine is approved for clinical use and used widely in treatment of Hepatitis B and AIDS either alone or in combination with another antiviral drugs because of its water solubility and shorter half -life (6 hours) drug requires frequent dosing by oral route, of various recent techniques for controlling drug release, matrix system offer various advantages of ease of formulation better control on release profile of drug and better patient compliance.
- The pronounced fluctuation resulting from the conventional drug administration are likely to yield period of therapeutic effects when the concentration falls below the minimum therapeutic drug concentration and can be controlled within the narrow therapeutic range by use of sustained release system. Which will minimize the severity of side effects.
- Hydrophilic and hydrophobic polymer matrix system are widely used for designing oral sustained release drug delivery dosage form because of their flexibility to provide a desirable drug release profile, cost effectiveness and broad regulatory acceptance.
- Large scale production needs more simplicity in the formulation with economic and cheapest dosage form. The matrix tablets formulation by direct compression method is most acceptable in large scale production.

**Objectives of the work are:**

- To evaluate the physical characters of prepared sustained release tablets
- To elucidate the effect of polymer composition, on the release kinetics and
- To determine the chemical compatibility of formulation containing various ratios of polymer and drug.

Lamivudine (β-L- 2', 3'-dideoxy-3'-thiacytidine), one of the dideoxy cytidine analogue NRTIs, is the first nucleoside analogue approved to treat chronic HBV infection and AIDS.

Conventional oral formulations of lamivudine are administered multiple times a day (150 mg twice daily) because of its moderate half-life ($t_{1/2}$ = 6 hours).

Treatment of AIDS using conventional formulations of lamivudine is found to have many drawbacks, such as adverse side effects resulting from accumulation of drug in multi-dose therapy, poor patient compliance, and high cost. Sustained release once-daily formulations of lamivudine can overcome some of these problems.

# PLAN OF WORK

# 3. PLAN OF WORK

The present work was carried out to design and evaluate sustained-release tablets of lamivudine, an anti retroviral drug. The sustained-release matrix tablets were prepared by direct compression method using HPMC K4M, ethyl cellulose, methyl cellulose, PVP K30, magnesium stearate and talc keeping in view the objectives described above the following plan of work was adopted.

**THE SCHEME OF THE ENTIRE WORK IS LISTED AS FOLLOWS:**

- Literature review
- Selection of drug and excipients
- Procurement of drug and excipients
- Physicochemical studies (organoleptic properties, melting point and solubility)
- Standardization of the method and construction of calibration curve for the estimation of lamivudine, quantification of drug.
- Compatibility studies of drug and polymer by FTIR spectral and DSC studies
- Formulation of lamivudine sustained release matrix tablets by using polymers like HPMC K4M, ethyl cellulose and methyl cellulose by direct compression method.

- Evaluation of blend characteristics of prepared granules (pre-compression parameters)
    i. Angle of repose
    ii. Determination of bulk density
    iii. Determination of tapped density
    iv. Compressibility index
    v. Hausner ratio
- Evaluation of physical parameters of lamivudine sustained-release tablets (post-compression parameters)
    i. Thickness and diameter
    ii. Hardness
    iii. Friability
    iv. Weight variation
    v. Drug content
- Evaluation of *in vitro* release characteristics of all formulations by using USP dissolution apparatus type I (Basket).
- To study the mechanism of drug release by applying kinetic parameters.
- To perform stability studies as per ICH guidelines.

# LITERATURE REVIEW

# 4. LITERATURE REVIEW

**Ahmed A., *et al.* (2008)** estimated the influence of EC with different viscosity grades on in vitro drug release from EC matrix tablets containing Indomethacin. Four viscosity grades were studied (7, 10, 50 and 100 cps). The drug release from the tablet is determined by dissolution testing as described in the USP. Based upon the pore characteristic studies which was determined by using helium pycnometry and mercury porosimetry the release rate constant has been found for different viscosity grades. From the result it is indicated the release rate is increased with an increase in viscosity grade.

**Amelia Avachat, *et al.* (2007)** was developed and characterized an oral controlled release drug delivery system for concomitant administration of diclofenac sodium (DS) and chondroitin sulfate (CS). A hydrophilic matrix-based tablet using different concentrations of hydroxypropyl methylcellulose (HPMC) was developed using wet granulation technique to contain 100 mg of DS and 400 mg of CS. Formulations prepared were evaluated for the release of DS and CS over a period of 9 hours in pH 6.8 phosphate buffer using United States Pharmacopoeia (USP) type II dissolution apparatus. Along with usual physical properties, the dynamics of water uptake and erosion degree of tablets were also investigated. The in vitro drug release study revealed that HPMC K100 CR at a concentration of 40% of the dosage form weight was able to control the simultaneous release of both DS and CS for 9 hours. The release of DS matched with the marketed CR tablet of DS with similarity factor (f2) above 50.

**Deepak S., *et al.* (2010)** had developed sustained release formulation of quetiapine fumarate using HPMC and PVP K30. The study involves fixing the drug

and polymer ratio for control the drug release up to the desired time. The effect of polymer concentration and polymer blend concentration were also studied. Dissolution studies were performed in 0.1N HCl for 2 hrs and in phosphate buffer up to 12 hours. From the release it was observed that the polymer blend of HPMC/PVP K30 were successfully sustained the release of drug up to 12 hrs.

**Gohel M.C.*, et al.* (2007)** was developed modified release of isoniazid using hydroxypropyl methylcellulose as a rate controlling agent. The low viscosity grade hydroxypropyl methylcellulose, medium viscosity grade hydroxypropyl methylcellulose and high viscosity grade Hydroxypropyl methylcellulose were used to prepare the matrix tablets. The tablets, prepared by direct compression, were subjected to physical characterization and *in-vitro* drug release studies. The release rate was strongly influenced by the type of polymer and concentration of polymer.

**Harris Shoaib M.*, et al.* (2006)** had formulated a once daily sustained release matrix tablet of ibuprofen using HPMC as release controlling factor and to evaluate drug release parameters as per various release kinetic models. The tablets were directly compressed using Avicel pH 101 and magnesium stearate. Different dissolution models were applied to drug release data in order to evaluate release mechanism. The drug release data fit well to the Higuchi expression.

**Indranil Kumar Yadav, *et al*. (2010)** was developed the oral sustained release matrix tablets of aceclofenac using hydrophilic and hydrophobic polymers. Aceclofenac is a non steroidal anti-inflammatory agent used in symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis and its biological half life is 4hrs. Controlled release formulations of aceclofenac (200 mg) were prepared by direct compression method. The tablets were subjected to physicochemical, in-vitro drug release and stability studies. The drug release from

optimized formulations F1, F4 and F7 was extended for a period of 12 hrs. The optimized formulations were subjected to stability studies for three months at 45°C temperature with RH 75±5%, and showed stability with respect to physicochemical parameters and release pattern. Results of the present study indicated the suitability of hydrophilic and hydrophobic polymers in the preparation of matrix based sustained release formulation of aceclofenac.

**Kalyani C., *et al.* (2009)** had designed oral sustained matrix tablets of zidovudine using HPMC K4M, guar gum and ethyl cellulose as the retardant polymers. Factors like polymer proportion, polymer type and effect of filler type on the in vitro release of the drug. The formulations were prepared by wet granulation technique. The granules were evaluated and all formulations showed compliance with pharmacopoeial standards. Formulation F2 and F8 sustained the release for 12 hrs. Formulation F5 was found to be best which contains 15% HPMC using MCC as diluent release 10 hours only.

**Kumar pal T., *et al.* (2007)** was designed an oral sustained release matrix tablet of metformin HCl and to optimize the drug release profile using response surface methodology. Tablets were prepared by non-aqueous wet granulation method using HPMC K15M as matrix forming polymer.

**Madhusmruti K., *et al.* (2010)** was developed sustain release matrix formulation of Propanolol hydrochloride and investigate the effects of both hydrophilic and hydrophobic polymer on *in-vitro* drug release. Matrix tablets were prepared by direct compression method using different concentrations of Hydroxypropyl methyl cellulose (HPMC) and Ethyl Cellulose (EC). Prepared formulations were subjected to various studies like hardness, friability, thickness, % drug content, weight variation, dynamic of water uptake and erosion etc. Tablets were

subjected to *in-vitro* drug release in 0.1N HCl (pH 1.2) for first 2 hours followed by phosphate buffer (pH 6.8) remaining time.

**Patil U.K., *et al.* (2008)** prepared and evaluated sustained release matrix tablet using natural polymers like pectin, guar gum and xanthan gum. Furosemide is used as the model drug and the formulations were compressed by a direct compression. The tablets were evaluated for physical characteristic and all the formulations were found to be in acceptable limits. Among the polymers guar gum was found to exhibit greater swelling index than pectin and xanthan gum.

**Paul J. Sheskey, *et al.* (1994)** was studied the effect of roller compaction in the dry granulation of a controlled-release (CR) matrix formulation containing methylcellulose or hydroxypropyl methylcellulose (HPMC), niacinamide, and magnesium stearate. The authors investigated the use of roller compaction to enhance material flow in CR tablet formulations and evaluated the effect of roller compaction variables, such as roller pressure and product recycle, on tablet physical characteristics and drug-release profiles.

**Prabu Moses, *et al.* (2010)** had formulated Ciprofloxacin controlled release matrix tablets using HPMC K100M, Guar gum, Carboxy methylcellulose, starch, polyvinyl pyrrolidone k30, magnesium stearate, isopropyl alcohol. Formulated tablets were taken to evaluation studies such as hardness, weight variation, friability, drug content and thickness.

**Raghuram Reddy K., *et al.* (2003)** had formulated once daily sustained release matrix tablets of nicorandil, a novel potassium channel openers used in the treatment of cardiovascular disease. The tablets are prepared by wet granulation technique using ethanolic solutions of ethylcellulose (EC), Eudragit RL-100, Eudragit RS-100, and polyvinyl pyrrolidone as granulating agents with hydrophilic matrix

materials such as HPMC, sodium carboxylic cellulose and sodium alginate. The granules were studied for physiochemical characteristics and for evaluation parameters. Granules showed good flow property and tablet formulations are all within official limits. From the dissolution studies the formulation F1 could extend the release for 24 hrs and thus it exhibited the most successful formulation of the study.

**Raju Manda, *et al.* (2010)** was developed a sustained release matrix tablet of aceclofenac using different natural polymers (Guar gum, Xanthan gum, Chitosan) in various proportions as release controlling factor by direct compression method. The *in vitro* dissolution study was carried out for 11 hours using United States Pharmacopoeia (USP) 1 Basket-type dissolution apparatus in 0.1N hydrochloric acid for first 2 hours and phosphate buffer pH 7.4 for 9 hours. The in vitro release study shows that only F9 formulation was releases the drug in a sustained manner for 11 hours. This study explored the optimum concentration and effect of polymer(s) on acelofenac release pattern from the tablet matrix for 11 hour period.

**Saleh M. Saidan, *et al.* (2005)** developed guar gum matrix tablets for oral controlled release of water-soluble Diltiazem hydrochloride prepared by using microcrystalline cellulose, starch, magnesium stearate and talc. In vitro drug release studies were performed using USP dissolution rate apparatus.

**Sandip B. Tiwari, *et al.* (2003)** had formulated Tramadol hydrochloride using hydrophilic and hydrophobic matrix system for controlled release. The effect of concentration of hydrophilic and hydrophobic polymers on the release rate of Tramadol was studied. Hydrophilic matrix tablets prepared by wet granulation technique, while hydrophobic matrix tablets prepared by melt granulation technique. In vitro dissolution studies were performed.

**Saravanabhavan Shanmugam, *et al*. (2010)** was developed sustained release matrix tablets of aceclofenac. The tablets were prepared with different ratios of hydroxypropyl methylcellulose K100M and ethylcellulose by wet granulation technique. The solubility study of the aceclofenac was conducted to select a suitable dissolution medium for in vitro drug release studies. In vitro dissolution study was carried out for all the formulation and the results compared with marketed sustained release tablets**.** The drug release from matrix tablets was found to decrease with increase in polymer ratio of hydroxypropyl methylcellulose as well as ethylcellulose. Formulation F3 exhibited almost similar drug release profile in different dissolution media as that of marketed tablets.

**Seema Pushkar, *et al.* (2009)** was developed the extended release tableted matrix devices for once daily dosing of diclofenac sodium, and their evaluation for performance and compliance with official pharmacopoeial and allied pharmaceutical requirements. The matrix tablets were prepared by drug incorporated polymer matrix, formulated using different combinations and ratios of hydroxypropyl methylcellulose (HPMC), sodium carboxy methylcellulose (Sodium CMC), and sodium alginate (NaAlg). Several preformulation trials were conducted to study the effect and optimization of various formulation and process parameters. The drug loaded polymeric matrices so prepared were compressed to tablets and studied for drug the release behaviour and comparative kinetic characterization along with six popular marketed brands of Diclofenac SR tablets. The formulated granules and tablets compressed complied with compendial and mechanistic requirements. The *in vitro* results shown a better release profile of formulated delivery system when compared to marketed brands extended up to 24 hours. The various formulations have shown an extended release up to 11 – 23 hours in different release environments.

**Sundaramoorthy K., *et al.* (2011)** had formulated monolithic matrix tablets of metformin hydrochloride as extended release tablets by employing ethyl cellulose polymer and the extended release characterization of the formulated tablets was investigated. Extended release matrix tablets containing 500 mg metformin hydrochloride were developed by changing concentration of drug: polymer (EC) in the ratio of 5:1, 5:2, 5:3 and 5:4 by direct compression. Formulations were optimized based on the acceptable tablet properties *in-vitro* and *in-vivo* drug release. The result of *in-vitro* and *in-vivo* drug release studies indicated that formulation (drug: polymer =5:3), was the most successful of the study and exhibited constant and extended release of metformin hydrochloride 99-100.5% release at the end of 10 hours compared with reference standard. A decrease in release of the drug was observed on increasing polymer ratio at certain level. The $t_{25\%}$, $t_{50\%}$ and $t_{90\%}$ drug release values were calculated from selected formulation F3 on every specified period of stability studies and comparison of both room and accelerated condition by statistical t-test, there was no difference between storage temperature. The formulation F3 was showed similar *in-vitro* and *in-vivo* drug release when compared to market sustained release tablet (F5M).

**Literature review indicating work carried out on selected drug lamivudine is given below:**

**Althaf A.S., *et al.* (2010)** was designed oral sustained release matrix tablets of lamivudine using hydroxypropyl methylcellulose and ethylcellulose as retardant polymers and to study the effect of various mixtures of drug and polymers on the release profile of the formulation. The in vitro studies revealed that the formulation F7 can be taken as an ideal or optimized formulation of sustained release tablets for 16 hours release as it fulfills all the requirements for sustained release tablet.

**Potu Apparao, *et al.* (2011)** had formulated and evaluated gum based sustained release matrix tablets of Lamivudine using different natural polymers such as Guar gum, Xanthan gum, Rosin gum, Pectin, and Sodium alginate taken at 30%, 40% and 50% of the total weight of the tablet. Lamivudine is a potent hydrophilic anti viral agent indicated for treatment of AIDS (Acquired Immunodeficiency Syndrome). All the formulations were able to retard the release of the drug beyond 18 hours except pectin and sodium alginate were unable to sustain the drug release from the matrix tablets. F5 (40% Xanthan Gum) formulation was selected as optimized formulation.

**Ranendra Narayan Saha, *et al.* (2007)** was designed oral controlled release matrix tablets of lamivudine using hydroxypropyl methylcellulose (HPMC) as the retardant polymer and to study the effect of various formulation factors such as polymer proportion, polymer viscosity, and compression force on the in vitro release of drug. In vitro release studies revealed that the release rate decreased with increase in polymer proportion and viscosity grade. Increase in compression force was found to decrease the rate of drug release. Matrix tablets containing 60% HPMC 4000cps were found to show good initial release (26% in first hour) and extended the release up to 16 hours. Matrix tablets containing 80% HPMC 4000cps and 60% HPMC 15000cps showed a first-hour release of 22% but extended the release up to 20 hours.

**Sudha T., *et al.* (2010)** was developed for the analysis of lamivudine and abacavir in the combined dosage form (Abamune-L). The method depends on the application of simultaneous equation to resolve the interference due to spectral overlapping. The analytical signals were measured at 270 and 289 nm using 0.1N HCl as a solvent. Regression analysis of Beer's plot showed good correlation in a general concentration range of 5-30µg/ml with correlation coefficient (r=0.9995) for

lamivudine, whereas abacavir concentration range 5-30µg/ml with correlation coefficient (r=0.9992). The results of analysis have been validated statistically by repeatability and recovery studies. The results were found satisfactory and reproducible. The method was applied successfully for the estimation of lamivudine and abacavir simultaneously in tablet form without the interference of excipients.

**Swati Jain, *et al.* (2011)** was developed oral controlled release matrix tablets of lamivudine having different proportion of Guar gum (retardant polymer) and studied the effect of formulation factor such as polymer proportion on the *in- vitro* release. The prepared granules were evaluated such as angle of repose, loose bulk density, tapped bulk density and compressibility index and satisfactory results were obtained. Compressed tablets were also evaluated for uniformity of weight, content of active ingredient, thickness, friability, hardness, swelling, erosion behaviour and *in-vitro* dissolution studies. All the formulations showed good results which were compliance with Pharmacopoeial standards. Matrix tablets containing 15% guar gum (Formulation F2) were found to show good initial release (21.34% in initial hour) and allowed sustained release up to 12 hours.

**Vyas S.P., *et al.* (2009)** was developed for simultaneous estimation of lamivudine and silymarin. The method employs formation and solving of simultaneous equation using 270.9 nm and 326.4 nm as two analytical wavelengths. Both the drugs obey Beer's Law in the concentration ranges employed for this method. Accuracy and reproducibility of the proposed method was statistically validated by recovery studies.

# DRUG AND EXCIPIENTS PROFILE

# 5. DRUG AND EXCIPIENTS PROFILE

**5.1. Drug profile:** *(IP2007; Goodman and Gilman's, 2001;* http: // en. wikipedia.org/wiki/Lamivudine; http: //www.rxlist.com/epivir-drug. htm)

**5.1.1. Lamivudine:**

Lamivudine is nucleoside reverse transcriptase inhibitor.

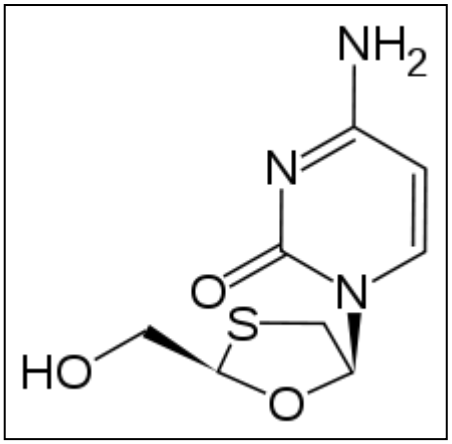
**Proprietary names :** EPIVIR, 3TC.

**Molecular formula :** $C_8H_{11}N_3O_3S$

**Molecular weight :** 229.3

**Chemical name :** 4-amino-1-[(2*R*, 5*S*)-2-(hydroxyl methyl)-1, 3-oxathiolan-5-yl]-1, 2-dihydropyrimidin-2-one.

**Structural formula:**




**Solubility :** It is soluble in water, sparingly soluble in methanol, and practically insoluble in acetone.

**Category :** Anti retroviral drug.

**Dose :** 150 mg per tablet twice daily.

**Melting point :** 172-178$^0$C

**pka** : 4.26

**$T_{max}$** : 0.5 - 1.5 hours.

**$C_{max}$** : 1.0 µg/ml.

**Volume of distribution** : 1.30 L/kg.

**Protein binding** : Less than 36%

**Biological half life** : 6 hours

**Bioavailability** : 86%.

**Description** : Lamivudine is a white or almost white powder, odorless, crystalline powder.

**Storage** : It should be kept in a well closed container, protected from light.

**Mechanism of action:**

Lamivudine is an analogue of cytidine. It can inhibit both types (1 and 2) of HIV reverse transcriptase and also the reverse transcriptase of hepatitis B. It is phosphorylated to active metabolites that compete for incorporation into viral DNA. They inhibit the HIV reverse transcriptase enzyme competitively and act as a chain terminator of DNA synthesis. The lack of a 3'-OH group in the incorporated nucleoside analogue prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA growth is terminated.

**Pharmacokinetic:**

Lamivudine is administered orally, and it is rapidly absorbed with a bio-availability of over 80%. Some research suggests that lamivudine can cross the blood-brain barrier.

**Adverse effects:**

The main adverse effect is severe abdominal or stomach pain, or feeling of fullness; nausea; tingling, burning, numbness, or pain in the hands, arms, feet, or legs; and vomiting.

**Drug interaction:**

Trimethoprim / sulfamethoxazole (Bactrim, Septra) and vitamins increases the concentration of lamivudine in the body.

**Pregnancy:** Use of lamivudine during pregnancy has not been adequately evaluated.

**Nursing mothers:**

It is not known whether lamivudine is secreted in breast milk. HIV infected mothers should not breast feed because of the potential risk of transmitting HIV to an infant that is not infected.

**Uses:**

Lamivudine is used for the treatment of HIV infection, prevention of HIV in those accidentally exposed to HIV, and the treatment of the hepatitis B infection.

**How to use:**

The recommended daily dose of lamivudine for adults is 300 mg once a day or 150 mg twice a day. For children 3 months to 16 years of age, the recommended dose is 4 mg/kg, up to a maximum of 150 mg twice a day. The recommended dose of lamivudine may be different for patients with decreased kidney function. Some individuals may benefit from different doses of lamivudine. Individuals should always take lamivudine as directed by their doctors. Lamivudine may be administered without regard to meals.

**Dosage forms:**

This medicine comes in the following strengths and forms:

- Lamivudine (Epivir-HBV) 100 mg tablets (for treating hepatitis B)
- Lamivudine 150 mg tablets (for treating HIV and AIDS)
- Lamivudine 300 mg tablets (for treating HIV and AIDS)
- Lamivudine (Epivir-HBV) oral solution (for treating hepatitis B) -- 5 mg of lamivudine per ml.
- Lamivudine oral solution (for treating HIV and AIDS) -- 10 mg of lamivudine per ml.

**5.2. Excipients profile:**

**5.2.1. Hypromellose:** ***(****Raymond C. R., et al., 2009)*

**Nonproprietary names:**

BP **:** Hypromellose

JP **:** Hydroxypropyl methylcellulose

PhEur **:** Hypromellosum

USP **:** Hypromellose

**Synonyms:**

Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropyl cellulose; Metolose; Tylopur.

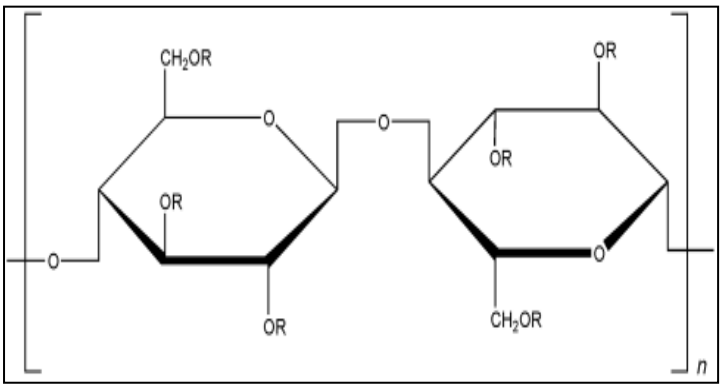
**Chemical name and CAS registry number:**

Cellulose 2- hydroxypropyl methyl ether [9004-65-3]

**Molecular weight:**

Molecular weight is approximately 10,000-1,500,000.

**Structural formula:**




Where R is H, $CH_3$, or $CH_3CH$ (OH) $CH_2$

**Functional category:**

Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder and viscosity increasing agent.

**Applications in pharmaceutical formulation or technology:**

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as matrix for use in extended-release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes.

High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10-80% w/w in tablets and capsules. Depending upon the viscosity grade, concentrations of 2-20% w/w are used for film-forming solutions to film-coat tablets.

Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents. Hypromellose at concentrations between 0.45-1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.

**Description:**

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

**Melting point:**

Browns at 190-200°C; chars at 225-230°C, glass transition temperature is 170-180°C.

**Moisture content:**

Hypromellose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air.

**Solubility:**

Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%) and ether but its soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol and other organic solvents.

**Viscosity (dynamic):**

A wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w.

**Stability and storage conditions:**

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3-11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol-gel transformation upon

heating and cooling, respectively. The gel point is 50-90°C, depending upon the grade and concentration of material.

**5.2.2. Ethyl cellulose:** ***(****Raymond C. R., et al., 2009)*

**Nonproprietary names:**

BP **:** Ethylcellulose

PhEur **:** Ethylcellulosum

USP **:** Ethylcellulose

**Synonyms:**

Aquacoat ECD; Aqualon; Ethocel.

**Chemical name and CAS registry number:**

Cellulose ethyl ether [9004-57-3]

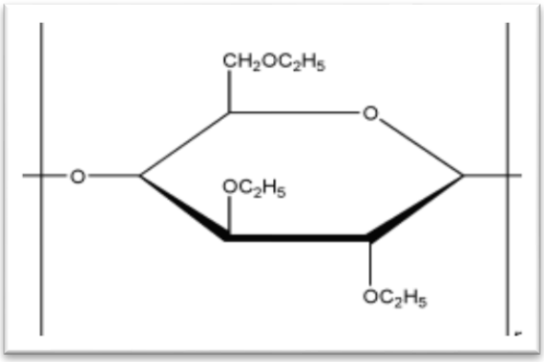
**Description:**

It is a tasteless, free flowing, white to light tan colored powder.

**Empirical formula and molecular weight:**

Ethyl cellulose with complete ethoxyl substitution (DS = 3) is $C_{12}H_{23}O_6$ ($C_{12}H_{22}O_5$) $nC_{12}H_{23}O_5$ where *n* can vary to provide a wide variety of molecular weights. Ethyl cellulose, an ethyl ether of cellulose, is a long-chain polymer of β-anhydroglucose units joined together by acetyl linkages.

**Structural formula:**



**Functional Category:**

Coating agent; flavoring fixative; tablet binder; tablet filler; viscosity-increasing agent.

**Solubility:**

Insoluble in water, glycerin, propylene glycol, ethyl cellulose that contains not less than 46.5% of ethoxyl group is freely soluble in chloroform, ethanol 95%, ethyl acetate, methanol and toluene.

**Viscosity:**

The viscosity of ethyl cellulose is determined at 25$^{o}$C by employing 5%w/w ethyl cellulose solubilized in a solvent ratio of 80% toluene: 20% ethanol. If increasing the viscosity of ethyl cellulose solution with an increase in ethyl cellulose concentration.

**Applications in pharmaceutical formulation or technology:**

Ethyl cellulose by itself forms a water insoluble coating for tablets and granules. It can improve the stability of a formulation. Modified release dosage form produced by incorporating of ethyl cellulose as a matrix material.

High viscosity grades of ethyl cellulose are used in microencapsulation process. For topical application it's used as a thickening agent in creams and lotions.

Ethyl cellulose it has been used as an agent for release the active compounds from oral appliances. Ethyl cellulose coated granules have the ability to absorb pressure and it will protect the coating layer from cracking during compression.

**Stability:**

It is chemically resistant to alkalis both dilute and concentrated but more sensitive to acidic materials than cellulose esters.

**5.2.3. Methyl cellulose:** *(Raymond C. R., et al., 2009)*

**Nonproprietary names:**

BP **:** Methylcellulose

PhEur **:** Methylcellulosum

USP **:** Methylcellulose

**Synonyms:**

Benecel; Culminal MC; E461; Methocel; Metolose.

**Chemical name and CAS registry number:**

Cellulose methyl ether [9004-67-5]

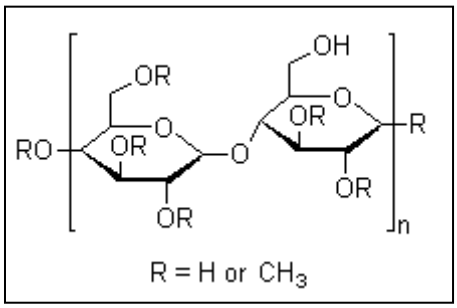
**Description:**

Methylcellulose occurs as a white, fibrous powder or granules. It is practically odorless and tasteless.

**Empirical formula and molecular weight:**

Methylcellulose is a long-chain substituted cellulose in which approximately 27–32% of the hydroxyl groups are in the form of the methyl ether. The various grades of methylcellulose have degrees of polymerization in the range 50–1000, with molecular weights (number average) in the range 10,000–2,20,000 Da. The degree of substitution of methylcellulose is defined as the average number of methoxyl (CH3O) groups attached to each of the anhydro glucose units along the chain. The degree of substitution also affects the physical properties of methylcellulose, such as its solubility.

**Structural formula:**




**Functional Category:**

Coating agent; emulsifying agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity increasing agent.

**Solubility:**

Practically insoluble in acetone, methanol, chloroform, ethanol (95%), ether, saturated salt solutions, toluene, and hot water. Soluble in glacial acetic acid and in a mixture of equal volumes of ethanol and chloroform. In cold water, methylcellulose swells and disperses slowly to form a clear to opalescent, viscous, colloidal dispersion.

**Viscosity:**

Various grades of methylcellulose are commercially available that vary in their degree of polymerization. Aqueous solutions at concentrations of 2% w/v will produce viscosities between 5 and 75,000 mPas. Individual grades of methylcellulose have a stated, narrowly defined viscosity range measured for a 2% w/v solution. The viscosity of solutions may be increased by increasing the concentration of methylcellulose. Increased temperatures reduce the viscosity of solutions until gel formation occurs at 50–60°C. The process of thermogelation is reversible, with a viscous solution being reformed on cooling.

**Applications in pharmaceutical formulation or technology:**

In tablet formulations, low- or medium-viscosity grades of methylcellulose are used as binding agents, the methylcellulose being added either as a dry powder or in solution. High viscosity grades of methylcellulose may also be incorporated in tablet formulations as a disintegrant. Methylcellulose may be added to a tablet formulation to produce sustained-release preparations.

Tablet cores may also be spray-coated with either aqueous or organic solutions of highly substituted low-viscosity grades of methylcellulose to mask an unpleasant taste or to modify the release of a drug by controlling the physical nature of the granules. Methylcellulose coats are also used for sealing tablet cores prior to sugar coating.

Low-viscosity grades of methylcellulose are used to emulsify olive, peanut, and mineral oils. They are also used as suspending or thickening agents for orally administered liquids, methylcellulose commonly being used in place of sugar-based syrups or other suspension bases. Methylcellulose delays the settling of suspensions and increases the contact time of drugs, such as antacids, in the stomach.

High-viscosity grades of methylcellulose are used to thicken topically applied products such as creams and gels.

In ophthalmic preparations, a 0.5–1.0% w/v solution of a highly substituted, high-viscosity grade of methylcellulose has been used as a vehicle for eye drops. However, hypromellose based formulations are now preferred for ophthalmic preparations.

Therapeutically, methylcellulose is used as a bulk laxative; it has also been used to aid appetite control in the management of obesity, but there is little evidence supporting its efficacy.

**Stability and storage:**

Methylcellulose powder is stable, although slightly hygroscopic. The bulk material should be stored in an airtight container in a cool, dry place.

**5.2.4. Cellulose, Microcrystalline:** *(Raymond C. R., et al., 2009)*

**Nonproprietary names:**

BP **:** Microcrystalline cellulose

JP **:** Microcrystalline cellulose

PhEur **:** Cellulosum microcristallinum

USPNF **:** Microcrystalline cellulose

**Synonyms:**

Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; Tabulose; Vivapur.

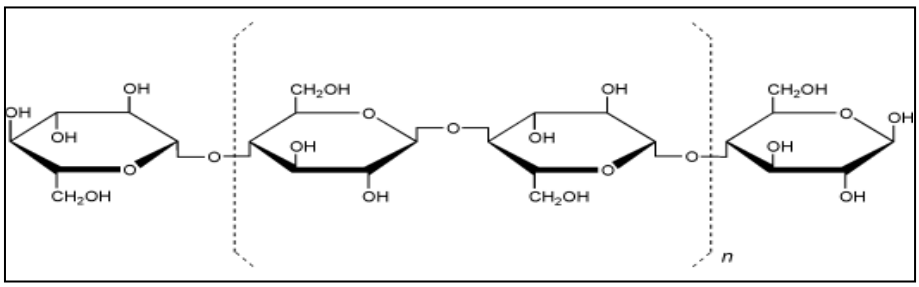
**Chemical name and CAS registry number:**

Cellulose [9004-34-6]

**Molecular weight:**

Approximately 36,000

**Structural formula:**




**Functional category:**

Adsorbent; suspending agent; tablet and capsule diluents; tablet disintegrant.

**Description:**

Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

**Moisture content:**

Typically less than 5% w/w. However, different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic.

**Solubility:**

Slightly soluble in 5% w/v sodium hydroxide solution, practically insoluble in water, dilute acids and most organic solvents.

**Applications in pharmaceutical formulation or technology:**

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as binder/diluents in oral tablet and capsule formulations where it is used in both wet-granulation and direct compression processes. In addition to its use as binder/diluents, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

| Use | Concentration (%) |
|---|---|
| Adsorbent | 20–90 |
| Antiadherent | 5–20 |
| Capsule binder/diluent | 20–90 |
| Tablet disintegrant | 5–15 |
| Tablet binder/diluent | 20–90 |

**Stability and storage conditions:**

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

**5.2.5. Povidone:** ***(****Raymond C. R., et al., 2009)*

**Nonproprietary names:**

BP **:** Povidone

JP **:** Povidone

PhEur **:** Povidonum

USP **:** Povidone

**Synonyms:**

E1201; Kollidon; Plasdone; poly [1-(2-oxo-1-pyrrolidinyl) ethylene]; polyvidone, polyvinyl pyrrolidone; 1-vinyl-2-pyrrolidinone polymer.

**Chemical name and CAS registry number:**

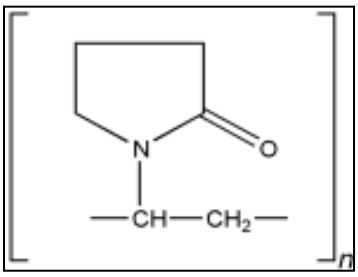
1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

**Empirical formula and molecular weight**

$(C_6H_9NO)_n$ and 2500-30,00,000 respectively.

| ***K*-value** | **Approximate molecular weight** |
|---|---|
| 12 | 2,500 |
| 15 | 8,000 |
| 17 | 10,000 |
| 25 | 30,000 |
| 30 | 50,000 |
| 60 | 4,00,000 |
| 90 | 10,00,000 |

**Structural formula:**




**Functional category:**

Disintegrant; dissolution aid; suspending agent; tablet binder.

**Description:**

Povidone occurs as a fine, white to creamy-white colored, odorless, hygroscopic powder.

**Moisture content:**

Povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidity.

**Solubility:**

Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol and water; practically insoluble in ether, hydrocarbons and mineral oil.

**Viscosity (dynamic):**

The viscosity of aqueous povidone solutions depends on both the concentration and the molecular weight of the polymer employed.

**Applications in pharmaceutical formulation or technology:**

Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet granulation processes. Povidone is also added to powder blends in the

dry form and granulated *in situ* by the addition of water, alcohol or hydro alcoholic solutions.

| Use | Concentration (%) |
|---|---|
| Carrier for drugs | 10–25 |
| Dispersing agent | Up to 5 |
| Eye drops | 2–10 |
| Suspending agent | Up to 5 |
| Tablet binder, tablet diluents or coating agent | 0.5–5 |

**Stability and storage conditions:**

Povidone darkens to some extent on heating at 150°C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–130°C; steam sterilization of an aqueous solution does not alter its properties.

**5.2.6. Magnesium stearate:** ***(****Raymond C.R., et al., 2009)*

**Nonproprietary names:**

BP **:** Magnesium stearate

JP **:** Magnesium stearate

PhEur **:** Magnesii stearas

USPNF **:** Magnesium stearate

**Synonyms:**

Magnesium octa decanoate, Magnesium salt.

**Chemical name and CAS registry number**

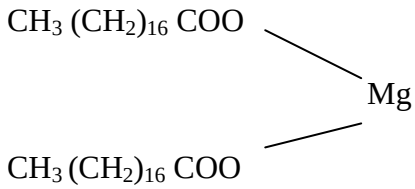
Octa decanoic acid magnesium salt [557-04-0]

**Functional category :** Tablet and capsule lubricant

**Empirical formula :** $C_{36}H_{70}MgO_4$

**Molecular weight :** 591.3

**Structure:**




**Description:**

It is a fine, white, precipitated or milled, impalpable powder of low bulk density and having a faint odor of stearic acid, characteristic taste.

**Solubility:**

It is insoluble in water, ethanol and ether. It can slightly soluble in warm ethanol and benzene.

**Stability and storage conditions:**

Stable, Store in a well closed container in a cool, dry place.

**5.2.7. Talc:** *(Raymond C. R., et al., 2009)*

**Nonproprietary names:**

BP **:** Purified talc

JP **:** Talc

PhEur **:** Talcum

USPNF **:** Talc

**Synonyms:**

Purified chalk, altalc, powdered talc and soapstone

**Chemical name and CAS registry number:**

Talc [14807-96-6]

**Description:**

A very fine, white to grayish white, impalpable, odorless crystalline powder, Unctuous, adheres readily to skin, soft to touch and free from granules.

**Empirical formula:**

$Mg_6 (Si_2O_5)_4(OH)_4$

**Functional category:**

Tablet, capsule it can use as a lubricant and diluents. During compression used as glidant and anticaking agent.

**Solubility:**

Insoluble in water, organic solvents, dilutes acids and alkalis.

**Storage conditions:**

Stable, Preserve in a well-closed container in a cool, dry place.

# MATERIALS AND EQUIPMENTS

# 6. MATERIALS AND EQUIPMENTS

## 6.1. Materials used:

**Table 6.1:** List of materials with source

| S.No. | Name of Ingredients | Name of supplier |
|---|---|---|
| 1 | Lamivudine | Shasun pharmaceuticals, Puducherry. |
| 2 | HPMC K4M | Tristar formulations Pvt. Ltd., Puducherry. |
| 3 | Ethyl cellulose | Tristar formulations Pvt. Ltd., Puducherry. |
| 4 | Methyl cellulose | Shasun pharmaceuticals, Puducherry. |
| 5 | Microcrystalline cellulose | Nickon laboratories Pvt. Ltd., Puducherry. |
| 6 | Polyvinyl pyrrolidone K30 | Nickon laboratories Pvt. Ltd., Puducherry. |
| 7 | Magnesium stearate | Loba chemie Pvt.Ltd., Mumbai. |
| 8 | Talc | Loba chemie Pvt.Ltd., Mumbai. |
| 9 | Hydrochloric acid | S d fine-chem limited, Mumbai. |
| 10 | Methanol | Qualigens fine chemicals, Mumbai. |
| 11 | Acetone | Loba chemie Pvt.Ltd., Mumbai. |
| 12 | Sodium hydroxide | S d fine-chem limited, Mumbai. |

## 6.2. Equipments used:

**Table 6.2:** List of equipments with model/make

| S.No. | Equipment | Model/ Make |
|---|---|---|
| 1 | Electronic balance | Shimadzu BL-220H, Japan. |
| 2 | Bulk density apparatus | Indolabs VTAP/MATIC-II, Chennai. |
| 3 | Standard sieves | Jayant scientific, India. |
| 4 | Hot air oven | Precision scientific Co., Chennai. |
| 5 | Sixteen punch tablet compression machine | Cadmach, Ahmadabad, India. |
| 6 | Friability apparatus | Veego scientific VFT-DV, Mumbai. |
| 7 | Hardness tester | Monsanto |
| 8 | Vernier caliper | Indolabs, Mitutoyo. |
| 9 | Humidity chamber | Labtech, Ambala. |
| 10 | USP dissolution test apparatus Type I | Veego scientific VDA-8DR, Mumbai. |
| 11 | UV-Visible spectrophotometer | Elico-SL 159 UV-Visible spectrophotometer, Japan. |
| 12 | FTIR spectrophotometer | Shimadzu, Japan. |
| 13 | Differential scanning calorimeter | Shimadzu, Japan. |

# *EXPERIMENTAL WORK*

# 7. EXPERIMENTAL WORK

## 7.1. Preformulation study:

Preformulation testing is an investigation of physical and chemical properties of a drug substance alone. It is the first step in rational development of dosage form.

### 7.1.1. Identification of drug:

**7.1.1.1. Identification by FTIR spectroscopy:** *(IP, 2007; Skoog D.A., et al., 2004)*

Lamivudine discs were prepared by pressing the lamivudine with potassium bromide and the spectra ranges between 4000 to 400 $cm^{-1}$ was obtained under the operational conditions. The absorption maximums in spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum.

**7.1.1.2. Identification by melting point:** *(IP, 2007)*

Melting point of the drug was determined by capillary tube method.

### 7.1.2. Physicochemical parameters:

**7.1.2.1. Organoleptic properties:** *(Lachman L., et al., 1991; Banker G.S., et al., 2009)*

The color, odor and taste of the drug were recorded using descriptive terminology.

**7.1.2.2. Solubility study:** *(IP, 2007)*

It is important to know about solubility characteristic of a drug in aqueous system, since they must possess some limited aqueous solubility to elicit a therapeutic response. The solubility of drug was recorded by using various descriptive terminology specified in Indian Pharmacopoeia, 2007.

**7.1.3. Analytical methods:**

**7.1.3.1. Determination of absorption maximum in 0.1 N HCl:** *(Sudha T., et al., 2010)*

A stock solution of lamivudine was prepared by dissolving 100 mg of drug in 0.1 N HCl and final volume was made to 100 ml. From the stock solution, 1 ml was pipettted out into 100 ml volumetric flask to obtain concentration of 10µg/ml. The solution was scanned in the range of wavelength of 200 to 400 nm region on shimadzu- 1700 pharmaspec UV- Visible spectrophotometer.

**7.1.3.2. Determination of absorption maximum in pH 6.8 phosphate buffer:** *(Sudha T., et al., 2010)*

A stock solution of lamivudine was prepared by dissolving 100 mg of drug in pH 6.8 and final volume was made to 100 ml. From the stock solution, 1 ml was pipettted out into 100 ml volumetric flask to obtain concentration of 10µg/ml. The solution was scanned in the range of wavelength of 200 to 400 nm regions on shimadzu- 1700 pharmaspec UV-Visible spectrophotometer.

**7.1.3.3. Preparation of standard curve of lamivudine in 0.1N HCl:** *(Sudha T., et al., 2010)*

A stock solution of lamivudine was prepared by dissolving 100 mg of drug in 0.1 N HCl and final volume was made to 100 ml to give a solution concentration 1000 µg/ml. From the stock solution, 10 ml was pipettted out into 100 ml volumetric flask to obtain concentration of 100µg/ml. From the standard stock solution of lamivudine, appropriate aliquots of 2.5, 5.0, 7.5, 10.0, 12.5 and 15.0 ml were pipetted out into 50 ml volumetric flask and final volume was made with 0.1 N HCl. To obtained concentration of 5, 10, 15, 20, 25 and 30 µg/ml. Absorbance spectra of each solution

against 0.1 N HCl as blank were measured at 281 nm using Elico-SL 159 UV-Visible spectrophotometer.

**7.1.3.4. Preparation of standard curve of lamivudine in pH 6.8 phosphate buffer:** *(Sudha T., et al., 2010)*

A stock solution of lamivudine was prepared by dissolving 100 mg of drug in pH 6.8 and final volume was made to 100 ml to give a solution concentration 1000 µg/ml. From the stock solution, 10 ml was pipettted out into 100 ml volumetric flask to obtain concentration of 100µg/ml. From the standard stock solution of lamivudine appropriate aliquots of 2.5, 5.0, 7.5, 10.0, 12.5 and 15.0 ml were pipetted out into 50 ml volumetric flask and final volume was made with pH 6.8. To obtained concentration of 5, 10, 15, 20, 25 and 30 µg/ml. Absorbance spectra of each solution against pH 6.8 as blank were measured at 271.5 nm using Elico-SL 159 UV-Visible spectrophotometer.

**7.1.3.5. Determination of Percentage purity of Drug:** *(Ravichandran V., et al., 2009)*

An accurately weighed 100 mg of lamivudine was dissolved in 100 ml of pH 6.8 phosphate buffer followed by mixing for 10 minutes. From the stock solution, 10 ml was pipettted out into 100 ml volumetric flask to obtain concentration of 100µg/ml. The solution was filtered through a 0.45µ membrane filter. From the above solution, aliquots of 0.6 ml were transferred to 10 ml volumetric flasks and final volume was made to 10 ml with pH 6.8 phosphate buffer and the absorbance of resultant solution was measured by using Elico-SL 159 UV-Visible spectrophotometer at 271.5 nm using pH 6.8 phosphate buffer as blank.

**7.1.4. Determination of drug-polymer compatibility:** *(Aulton M.E., 2007)*

Differential scanning calorimetry, Fourier transforms infrared spectroscopy studies were used for the evaluation of physicochemical compatibility and interaction, which helps in the prediction of interaction of the drug and polymers. Each polymer used in the formulations was blended with the drug levels that are realistic with respect to the final dosage form. Each polymer was thoroughly blended with drug to increase drug- polymer molecular contacts to accelerate the reactions if possible.

**7.1.4.1. Fourier transform infrared spectroscopy:** *(Althaf A.S., et al., 2010; Raju M.,et al., 2010; Silverstein R.M., 2003)*

FTIR studies are very helpful in the evaluation of drug polymer interaction studies. If there is any incompatibility between the drug and polymer, these can be predicted by changes in the functional peaks. Infrared spectrum of lamivudine was determined on Fourier transform infrared spectrophotometer using potassium bromide dispersion method. The base line correction was done using dried potassium bromide. Then the spectrum of dried mixture of drug and various polymers were thoroughly mixed with potassium bromide. The crushed powders were compressed using a hydraulic compactor at approximately 20,000 pounds under vacuum for 3 minutes. FTIR instrument were performed under nitrogen atmosphere at a flow rate of 50 standard cubic feet per hour. Spectral scanning was conducted from 4000 to 400 $cm^{-1}$ at a resolution of 4 $cm^{-1}$ by using Shimadzu (Japan) FTIR spectrophotometer.

**7.1.4.2. Differential scanning calorimetry:** *(Raju M.,et al., 2010; Willard H.H., et al., 2008)*

Any possible drug polymer interaction can be studied by thermal analysis. The DSC analysis of pure drug, drug + HPMC K4M, drug + methyl cellulose and drug + ethyl cellulose were carried out using Shimadzu to evaluate any possible drug-

polymer interaction. The 2 mg sample were heated in a hermetically sealed aluminum pans in the temperature range of 25-300ºC at heating rate of 10ºC /min under nitrogen flow of 30 ml/min.

**7.1.5. Formulation of lamivudine sustained release matrix tablets:** *(Swati jain, et al., 2011)*

All the ingredients mentioned in Table 7.1 were pre-weighed and passed through mesh #60 separately. The drug and polymer were blended first in mortar and pestle then the remaining ingredients are added in that and blended for 15 minutes and the blend is finally passed through mesh #20 and used for evaluation of flow characteristic.

**Table 7.1:** Composition of lamivudine SR matrix tablets

| Ingredients | LF1 | LF2 | LF3 | LF4 | LF5 | LF6 | LF7 | LF8 | LF9 |
|---|---|---|---|---|---|---|---|---|---|
| **Lamivudine** | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |
| **HPMC K4M** | 40 | 80 | 120 | - | - | - | - | - | - |
| **Methyl cellulose** | - | - | - | 40 | 80 | 120 | - | - | - |
| **Ethyl cellulose** | - | - | - | - | - | - | 40 | 80 | 120 |
| **Microcrystalline-cellulose PH 102** | 128 | 88 | 48 | 128 | 88 | 48 | 128 | 88 | 48 |
| **Polyvinyl pyrrolidone-k30** | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| **Magnesium stearate** | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| **Talc** | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| **Total weight** | **400** | **400** | **400** | **400** | **400** | **400** | **400** | **400** | **400** |

All the quantities are expressed as mg per tablet.

### 7.1.6. Evaluation of pre-compression blend:

#### 7.1.6.1. Angle of repose: *(Lachman L., et al., 1991)*

The angle of repose was determined by the funnel method. An accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured. The angle of repose was calculated using the following equation.

$$\tan(\theta) = \frac{h}{r}$$

Where '**h**' and '**r**' are the height and radius respectively of the powder cone.

**Table 7.2:** Standard values of angle of repose (°)

| S. No. | Flowability | Angle of repose |
|---|---|---|
| **1** | Excellent | <25 |
| **2** | Good | 25-30 |
| **3** | Passable* | 30-40 |
| **4** | Poor | 37-45 |
| **5** | Very poor | >45 |

* Adding glidant for improving flow

#### 7.1.6.2. Loose bulk density: *(Lachman L., et al., 1991)*

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced in to a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. The loose bulk density of powder blends was determined using the following formula.

**Loose bulk density = Total weight of powder / Total volume of powder**

**7.1.6.3. Tapped bulk density:** *(Lachman L., et al., 1991)*

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The tapped bulk densities of powder blends were determined using the following formula.

**Tapped bulk density= Total weight of powder / Total volume of tapped powder**

**7.1.6.4. Hausner's ratio:** *(Aulton M.E., 2007)*

It is related to interparticulate friction and could be used to predict powder flow properties. Hausner's ratio was determined by following equation,

**Hausner's Ratio = Tapped bulk density / Loose bulk density**

A Hausner ratio less than 1.25 indicates good flow while greater than 1.5 indicates poor flow.

**7.1.6.5. Carr's compressibility index:** *(Aulton M.E., 2007)*

It is a simple index that can be determined on small quantities of powder. The compressibility indices of the powder blends was determined using following formula,

**Carr's compressibility index (%) = [(TBD-LBD)/ TBD] x100**

Relationship between % compressibility and flowability is shown in the table 7.3.

**Table 7.3:** Standard values of Carr's index

| S. No. | Carr's index | Type of flow |
|---|---|---|
| **1** | 5-15 | Excellent |
| **2** | 12-16 | Good |
| **3** | 18-21 | Fair to passable |
| **4** | 23-35 | Poor* |
| **5** | 33-38 | Very poor* |
| **6** | >40 | Extremely poor* |

* May be improved by glidant

**7.2.** P**reparation of SR Matrix Tablets:** *(Potu Apparao, et al., 2011)*

**Direct compression method:**

All the ingredients metioned in Table 7.1 were passed through Sieve no. 60 mesh separately and collected. Ingredients were mixed in geometrical order and thoroughly mixed for 15 minutes to get a uniform mixture and the blend is finally passed through mesh #20. Talc and magnesium stearate were added to the powder mixture and compressed on a 16- station rotary tablet compression machine using 11mm round, biconcave punches.

The drug polymer ratio was developed to adjust drug release as per theoretical release profile and to keep total weight of tablet constant for all the fabricated batches under experimental conditions of preparations. The total weight of the matrix tablets was 400 mg with different drug polymer ratios like 1:0.2, 1:0.4, and 1:0.6. The various polymers used were hydroxypropyl methylcellulose (HPMC K4M), methyl cellulose and ethyl cellulose.

In the formulations prepared, the release retardants included were hydroxypropyl methylcellulose (HPMC K4M), ethyl cellulose and methyl cellulose.

Microcrystalline cellulose (MCC) is used as diluent. Magnesium stearate 1% and talc 2 % were used as lubricant and glidant.

**7.3. Evaluation of lamivudine sustained release matrix tablets:**

**7.3.1. Appearance:** *(Lachman L., et al., 1991)*

The tablets were visually observed for capping, chipping and lamination.

**7.3.2. Dimension (Thickness and Diameter):** *(Lachman L., et al., 1991)*

The thickness and diameter of tablets were important for uniformity of tablet size. The thickness and diameter of the tablets was determined by using Vernier caliper. Ten tablets from each type of formulation were used and average values were calculated.

**7.3.3. Tablet hardness:** *(Lachman L., et al., 1991)*

For each formulation, the hardness of 10 tablets was determined using the Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm$^2$. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg/cm$^2$.

**7.3.4. Percent friability:** *(Lachman L., et al., 1991)*

Friability is the measure of tablet strength. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of pre weighed tablets was placed in Roche friabilator which was then operated for 100 revolutions. The tablets were then dedusted and reweighed. A loss of less than 1 % in weight is generally considered acceptable. Percent friability (% F) was calculated as follows.

$$\%\text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

**7.3.5. Weight variation:** *(IP, 2007; Lachman L., et al., 1991)*

To find out weight variation 20 tablets of each formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight. The test was performed according to the official method.

Weight variation importance during tablets compression section, each and every time intervals we must check the weight of tablet. If we are not maintaining the weight variation means it will give the deviation of drug content as well as yield of tablets.

**Table 7.4:** Specifications of % weight variation allowed in tablets as per Indian Pharmacopoeia

| S. No. | Average weight of tablets (mg) | Maximum percent deviation allowed (%) |
|---|---|---|
| 1 | 80 or less | 10 |
| 2 | More than 80 but less than 250 | 7.5 |
| 3 | More than 250 | 5 |

**7.3.6. Drug content:** *(Swati jain, et al., 2011; http://www.who.int)*

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to 100 mg of lamivudine was transferred into a 100 ml standard volumetric flask. Then added 50ml of pH 6.8 phosphate buffer solution. It was gently shaken for 15 minutes. Then made upto the mark with pH 6.8 phosphate buffer solution. The solution was filtered through a whatmann filter paper, diluted suitably and the absorbance of resultant solution was measured by using Elico-SL 159 UV-Visible spectrophotometer at 271.5 nm using pH 6.8 phosphate buffer as blank.

**7.3.7. *In vitro* release studies:** *(Potu Apparao., et al., 2011)*

The release rate of lamivudine from matrix tablets was determined using United States Pharmacopoeia dissolution testing apparatus I (Basket method; Veego Scientific VDA-8DR, Mumbai, India). The dissolution test was performed at 100 rpm using 900 ml of pH 1.2 for the first 2 hrs and phosphate buffer pH 6.8 from 2-12 hrs at 37 ± 0.5°C. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted suitably. Absorbance of these solutions was measured at 271.5 nm using Elico-SL 159 UV-Visible spectrophotometer. For each formulation, the experiments were carried out in triplicate. The release data were analyzed to study the release kinetics using zero order, first order and matrix, korsmeyer-peppas equations by using PCP disso V3 software.

**7.3.8. Kinetics of *in vitro* drug release:** *(Brahmankar D.M. and Jaiswal S.B., 2009; Harris S.M., et al., 2006)*

To study the release kinetics of *in vitro* drug release, the data was applied to kinetic models such as zero order, first order, higuchi and korsmeyer- Peppas.

- **Zero order**

$$C = K_0 t$$

Where $K_0$ - Zero-order rate constant expressed in units of concentration/time

t - Time in hrs.

- **First order**

$$LogC = LogC_0 - Kt / 2.303$$

Where $C_0$ - Initial concentration of drug,

K - First order constant and t - Time in hrs.

- **Higuchi**

$$Q_t = Kt^{1/2}$$

Where $Q_t$ - Amount of the release drug in time t,

K- Kinetic constant and t- is time in hrs

- **Korsmeyer Peppas**

$$M_t / M_\infty = Kt\ n$$

Where, Mt - represents amount of the released drug at time t,

$M_\infty$- Overall amount of the drug (whole dose) released after 12 hrs

K- Diffusion characteristic of drug/ polymer system constant

n- Diffusion exponent that characterizes the mechanism of release of drug.

**Table 7.5:** Diffusion exponent and solute release mechanism

| Diffusion exponent (n) | Overall solute diffusion mechanism |
|---|---|
| **0.45** | Fickian diffusion |
| **0.45<n <0.89** | Anomalous (non-Fickian) diffusion |
| **0.89** | Case-II transport |
| **n>0.89** | Super case-II transport |

**7.4. Stability study:** *(Carstensen J.T., et al., 2008; Manavalan R., et al., 2008)*

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted.

ICH specifies the length of study and storage conditions

- **Long-Term Testing**: 25°C ± 2°C at 60% RH ± 5% for 12 Months
- **Accelerated Testing:** 40°C ± 2°C at 75% RH ± 5% for 6 Months

In present study the selected formulation LF3 exposure up to 3 months stability studies at accelerated condition (40°C ± 2°C at 75% RH ± 5% RH) to find out the effect of aging on hardness, drug content and *in vitro* drug release.

Stability studies were carried out at accelerated condition (40°C ± 2°C at 75% RH ± 5% RH) for the optimized formulation LF3. The matrix tablets were stored at 40°C ± 2°C at 75% RH ± 5% RH for accelerated temperature in closely packed with aluminium foil for 3 months. The samples were withdrawn after periods of 1st month, 2nd month and 3rd month. The samples were analyzed for its hardness, drug content and *in vitro* drug release.

# RESULTS AND DISCUSSION

# 8. RESULTS AND DISCUSSION

## 8.1. Preformulation parameters:

### 8.1.1. Identification of drug:

#### 8.1.1.1. Identification by FTIR spectroscopy:

The FTIR spectrum of lamivudine was shown in Figure 8.1 and the interpretations of FTIR frequencies were showed in Table 8.1.

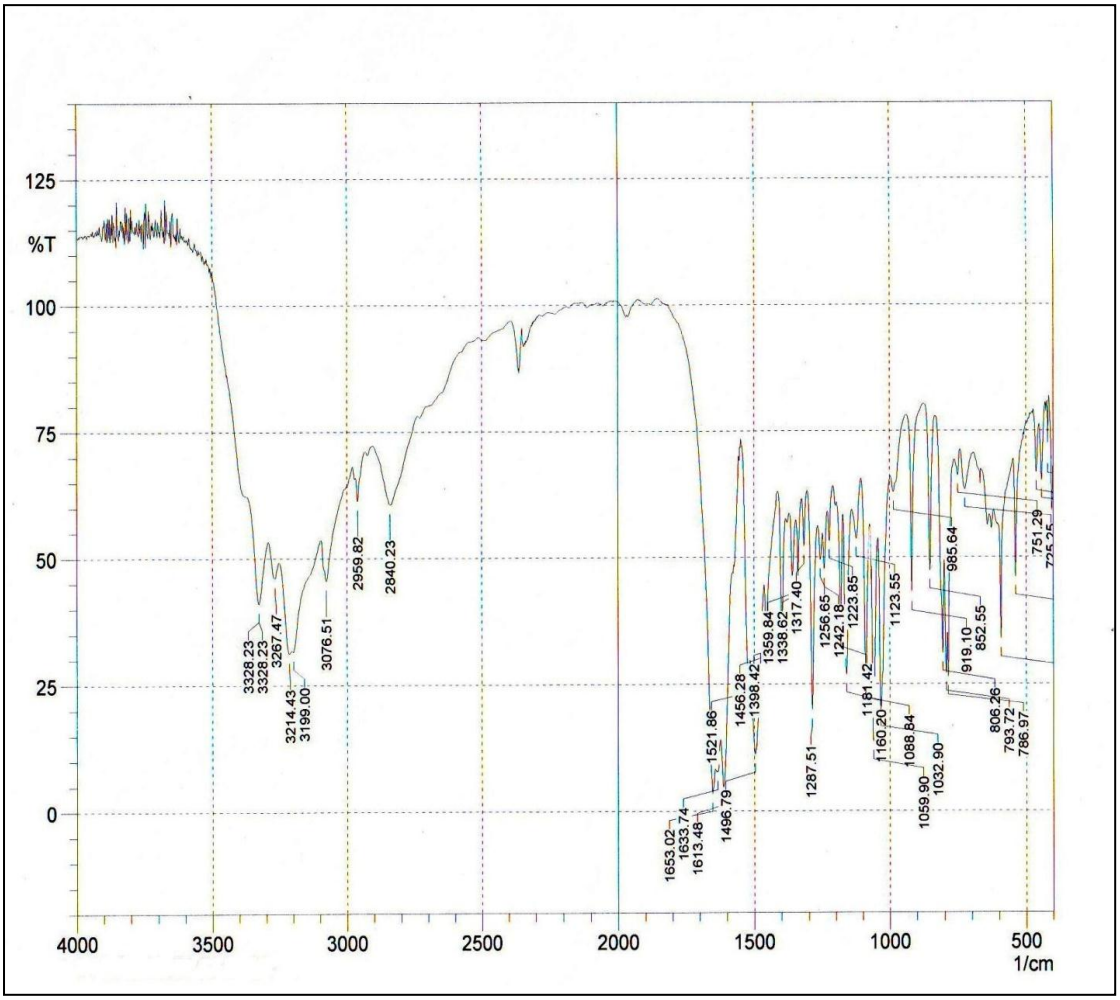



**Figure 8.1:** FTIR spectrum of lamivudine

- **Interpretation of FTIR Spectrum:**

Major functional groups present in lamivudine shows characteristic peaks in FTIR spectrum. Table 8.1 shows peaks observed at different wave numbers and the

functional group associated with these peaks. The major peaks are identical to functional group of lamivudine. Hence, the sample was confirmed as lamivudine.

**Table 8.1:** Characteristic frequencies in FTIR spectrum of lamivudine

| **Wave No.($cm^{-1}$)** | **Functional group** |
|---|---|
| 3328.23 | O-H stretching |
| 3076.51 | N-H stretching |
| 2840.23 | C-H stretching |
| 1653.02 | C=O stretching |
| 1613.48 | C=N stretching |
| 1521.86 | C=C stretching |
| 1287.51 | C-N stretching |
| 1088.84 | C-O stretching |
| 852.55 | C-C stretching |
| 786.97 | C-S stretching |

**8.1.1.2. Melting point:**

Melting point of lamivudine sample was found to be $174^0$C. The reported melting point for lamivudine was in range of 172 to $178^0$C. Hence, experimental values are in good agreement with official values.

**8.1.2. Physicochemical parameters of drug:**

**8.1.2.1. Organoleptic properties:**

**Odour :** Odorless

**Colour :** A White (or) almost white powder

**Taste :** Bitter taste

### 8.1.2.2. Solubility study:

**Table 8.2:** Solubility of lamivudine in different solvents

| Name of solvents | Solubility |
|---|---|
| Distilled water | Soluble |
| Methanol | Sparingly soluble |
| 0.1N HCl | Soluble |
| 0.1 N NaOH | Soluble |
| Phosphate buffer (pH 6.8) | Soluble |
| Phosphate buffer (pH 7.4) | Soluble |
| Acetone | Practically insoluble |

### 8.1.3. Analytical methods:

### 8.1.3.1. Determination of absorption maximum in 0.1 N HCl:

The absorption maximum for lamivudine was found to be 281 nm.

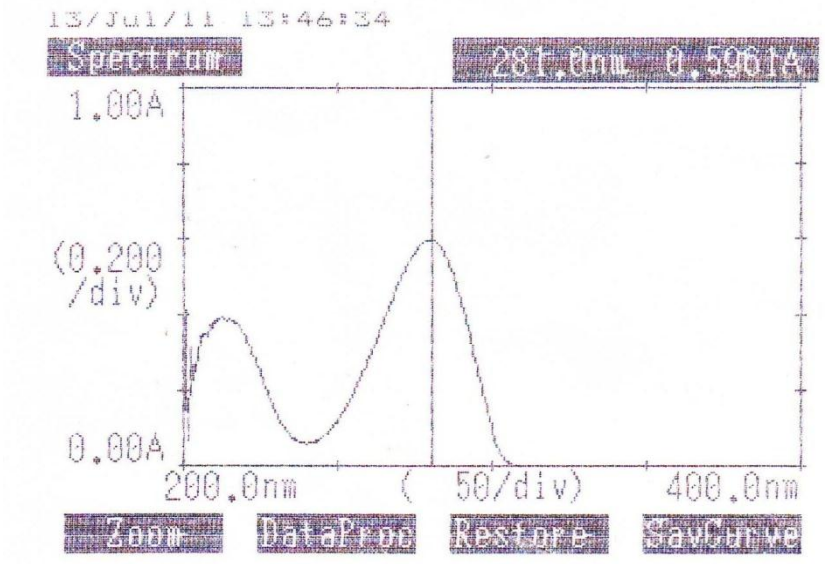



**Figure 8.2:** $\lambda_{max}$ observed for lamivudine in 0.1N HCl

### 8.1.3.2. Determination of absorption maximum in pH 6.8 phosphate buffer:

The absorption maximum of lamivudine was found to be 271.5 nm.


**Figure 8.3:** $\lambda_{max}$ observed for lamivudine in pH 6.8 phosphate buffer.

### 8.1.3.3. Preparation of standard curve of lamivudine in 0.1 N HCl:

UV absorption spectrum of lamivudine in 0.1N HCl showed $\lambda_{max}$ at 281 nm. Absorbance obtained for various concentrations of lamivudine in 0.1N HCl are given in Table 8.3. The curve of absorbance versus concentration for lamivudine was found to be linear in the concentration range of 5–30 µg/ ml. The drug obeys Beer-Lambert's law in the range of 5–30 µg/ ml.

**Table 8.3:** Concentration and absorbance of lamivudine 0.1N HCl

| S. No. | Concentration (µg/ml) | Absorbance |
|---|---|---|
| 1 | 0 | 0.000 |
| 2 | 5 | 0.304 |
| 3 | 10 | 0.597 |
| 4 | 15 | 0.901 |
| 5 | 20 | 1.173 |
| 6 | 25 | 1.472 |
| 7 | 30 | 1.760 |

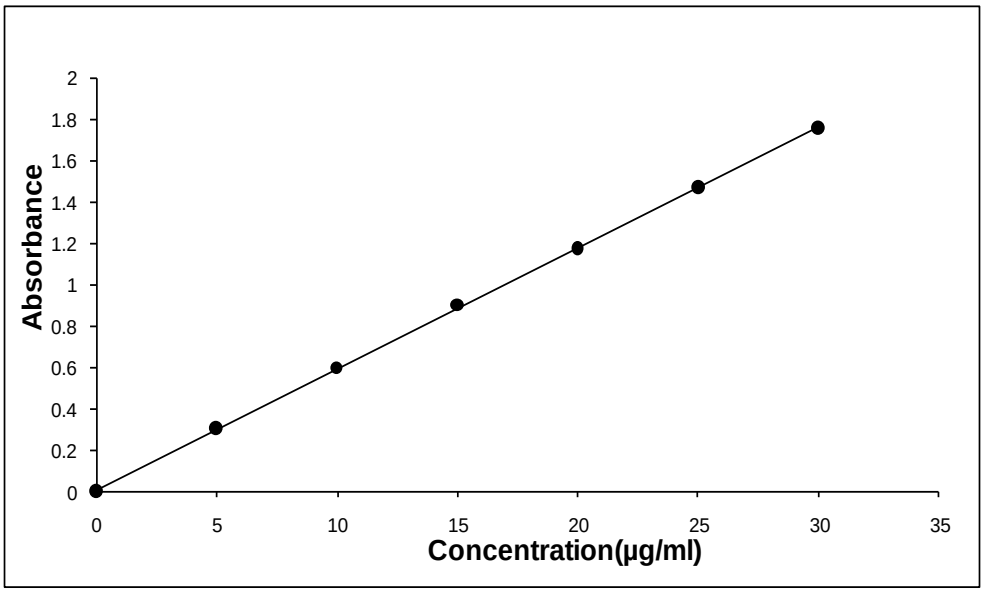



**Figure 8.4:** Calibration curve of lamivudine in 0.1N HCl

**Table 8.4:** Calibration parameter values in 0.1 N HCl

| S. No. | Parameters | Values |
|---|---|---|
| 1 | Correlation coefficient (r) | 0.9999 |
| 2 | Slope (m) | 0.0585 |
| 3 | Intercept (c) | 0.0090 |

**8.1.3.4. Preparation of standard curve of lamivudine in pH 6.8 phosphate buffer:**

UV absorption spectrum of lamivudine in pH 6.8 showed $\lambda_{max}$ at 271.5 nm. Absorbance obtained for various concentrations of lamivudine in pH 6.8 are given in Table 8.5. The curve of absorbance versus concentration for lamivudine was found to be linear in the concentration range of 5–30 µg/ ml. The drug obeys Beer- Lambert's law in the range of 5–30 µg/ ml.

**Table 8.5:** Concentration and absorbance of lamivudine in pH 6.8 phosphate buffer

| S. No. | Concentration (µg/ml) | Absorbance |
|---|---|---|
| 1 | 0 | 0.000 |
| 2 | 5 | 0.210 |
| 3 | 10 | 0.409 |
| 4 | 15 | 0.592 |
| 5 | 20 | 0.788 |
| 6 | 25 | 0.981 |
| 7 | 30 | 1.183 |

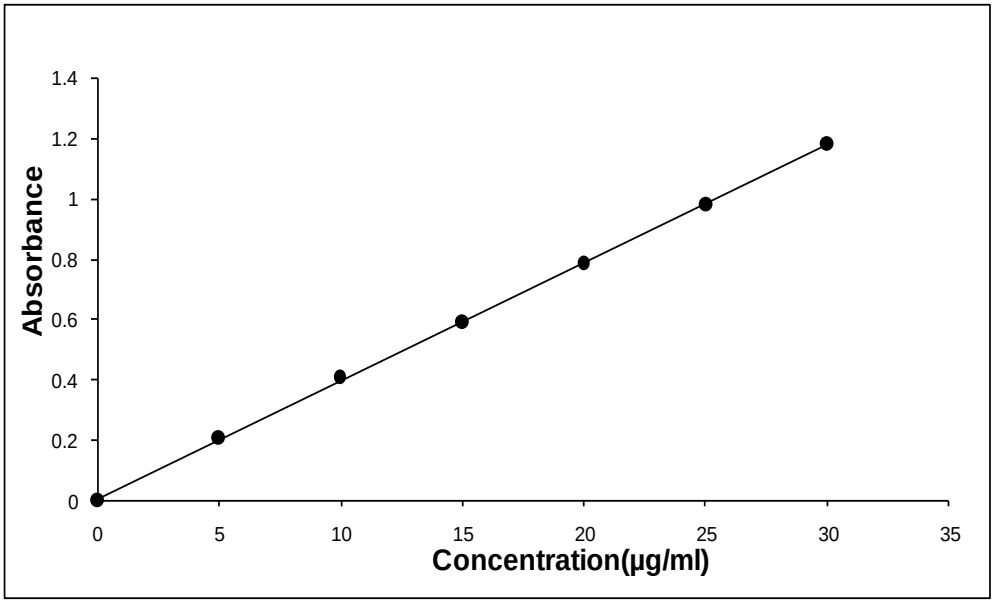



**Figure 8.5:** Calibration curve of lamivudine in pH 6.8 phosphate buffer

**Table 8.6:** Calibration parameter values in pH 6.8 phosphate buffer

| S. No. | Parameters | Values |
|---|---|---|
| 1 | Correlation coefficient (r) | 0.9999 |
| 2 | Slope (m) | 0.0391 |
| 3 | Intercept (c) | 0.0086 |

**8.1.3.5. Percentage purity of drug:**

The percentage purity of drug was calculated by using calibration curve method. The percentage purity of drug was found in official limits.

**Table 8.7:** Percentage purity of lamivudine in pure drug

| S. No. | Percentage purity (%) | Average percentage purity (%) |
|---|---|---|
| 1 | 99.79 | 100.13 ± 0.30 |
| 2 | 100.29 | |
| 3 | 100.33 | |

The reported percentage purity for lamivudine in IP 2007 is 97 to 102%.

**8.1.4. Compatibility testing of drug with polymer:**

Compatibility of drug and polymers was found to be as following methods such as Fourier transform infrared spectroscopy and differential scanning calorimetry.

**8.1.4.1. Fourier transform infrared spectroscopy:**

The FTIR spectrums of lamivudine with different polymers used in formulation are shown in Figures 8.6, 8.7, 8.8 and Table 8.8.

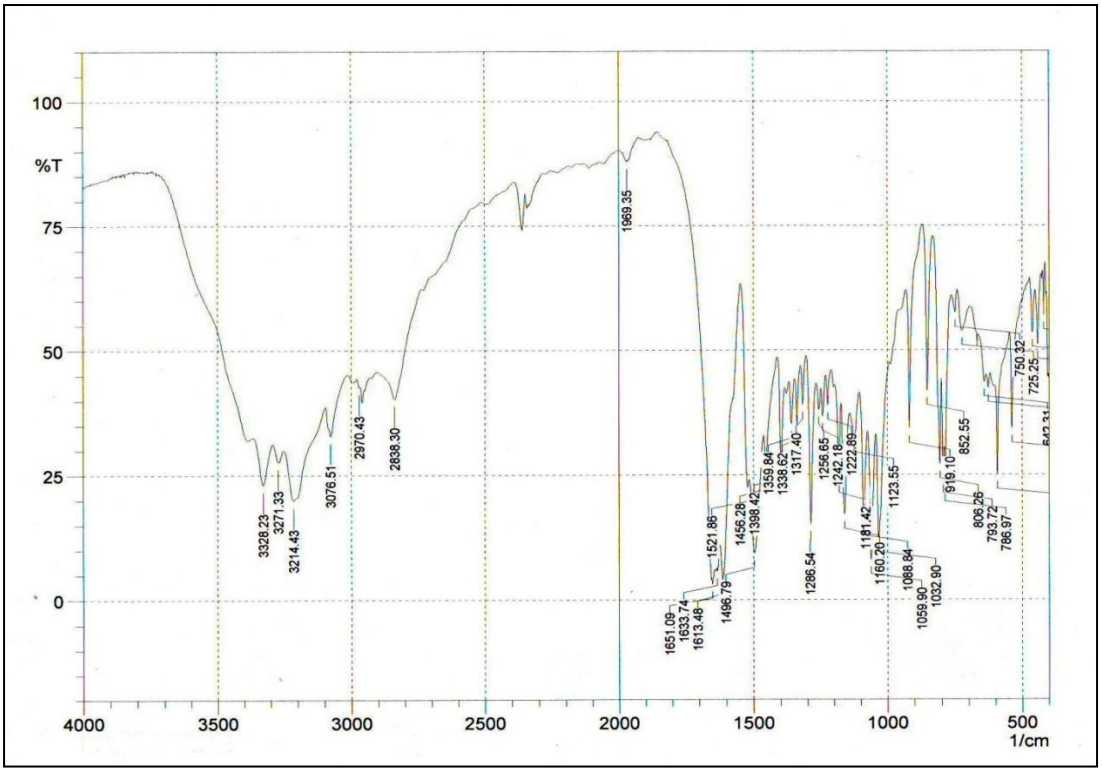



**Figure 8.6:** FTIR spectrum of lamivudine + HPMC K4M

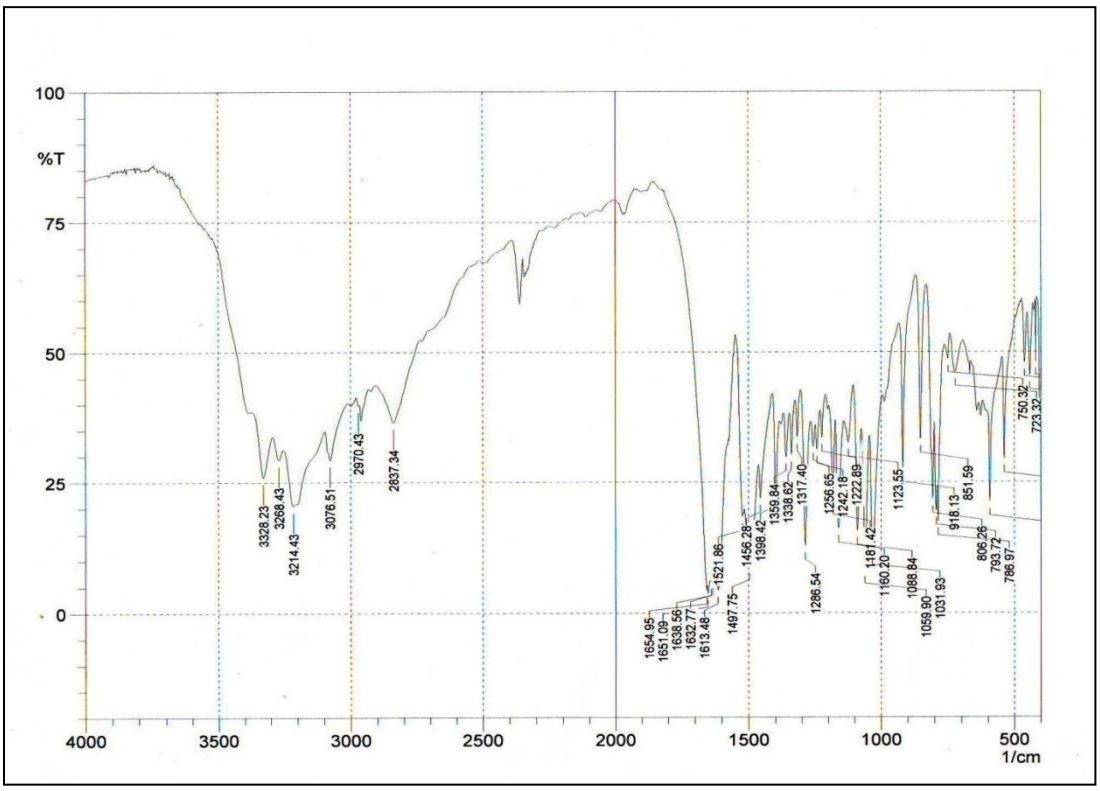



**Figure 8.7:** FTIR spectrum of lamivudine + methyl cellulose

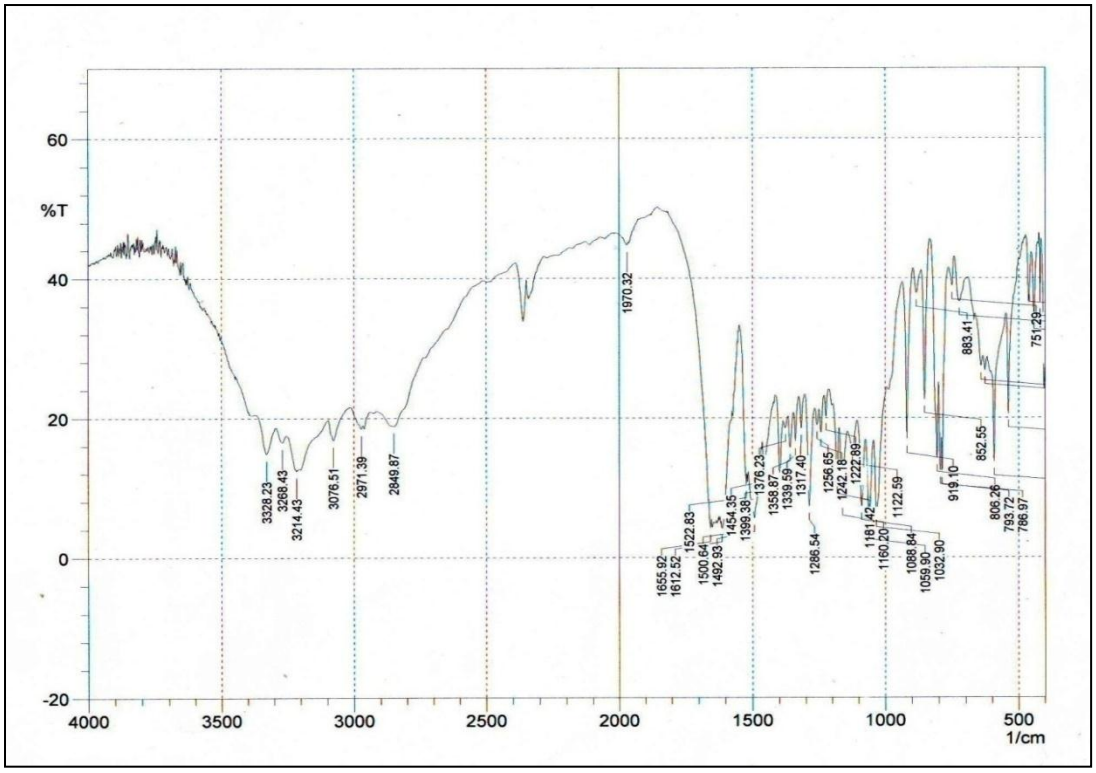



**Figure 8.8:** FTIR spectrum of lamivudine + ethyl cellulose

**Table 8.8:** FTIR peak observed for lamivudine with different polymers used in formulations.

| Functional groups | Peaks observed [Wave No. ($cm^{-1}$)] | | |
|---|---|---|---|
| | **LAM + HPMC K4M** | **LAM + Methyl cellulose** | **LAM + Ethyl cellulose** |
| O-H stretching | 3328.23 | 3328.23 | 3328.23 |
| N-H stretching | 3076.51 | 3076.51 | 3076.51 |
| C-H stretching | 2838.30 | 2837.34 | 2849.87 |
| C=O stretching | 1651.09 | 1651.09 | 1655.92 |
| C=N stretching | 1613.48 | 1613.48 | 1612.52 |
| C=C stretching | 1521.86 | 1521.86 | 1522.83 |
| C-N stretching | 1286.54 | 1286.54 | 1286.54 |
| C-O stretching | 1088.84 | 1088.84 | 1088.84 |
| C-C stretching | 852.55 | 851.59 | 852.55 |
| C-S stretching | 786.97 | 786.97 | 786.97 |

According to Table 8.1 and 8.8 and Figures 8.1, 8.6, 8.7 and 8.8, FTIR spectrum showed that there was no major difference in peak when compared between pure drug of lamivudine and lamivudine with different polymers. Therefore it could indicate that there was no incompatibility between drug and different polymers.

**8.1.4.2. Differential scanning calorimetry:**

The compatibility and interactions between drug and polymers were checked using differential scanning calorimetry and the results were shown in Figures 8.9, 8.10, 8.11 and 8.12.

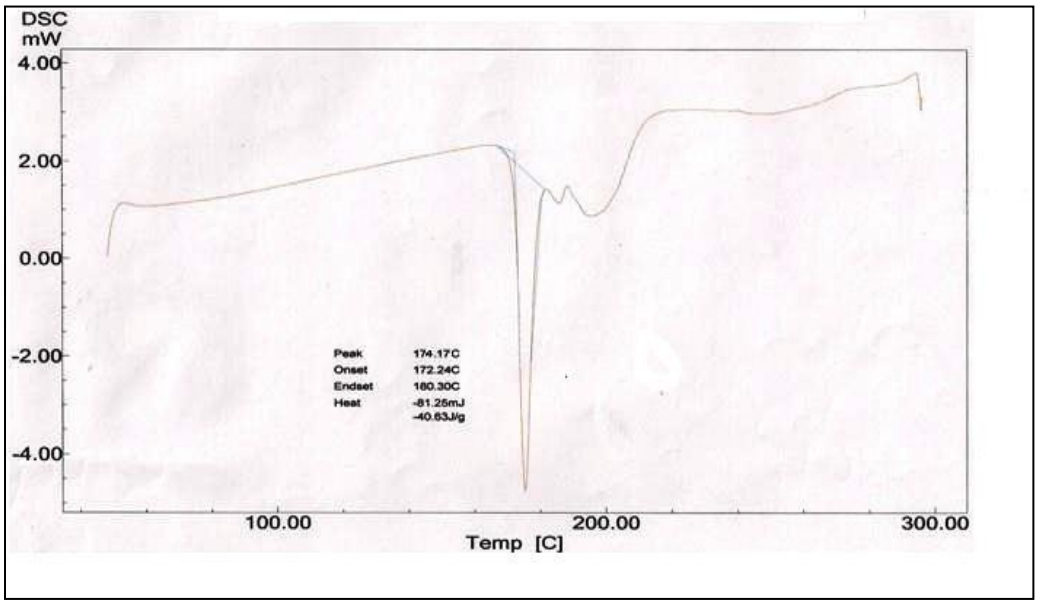



**Figure 8.9:** DSC thermal analysis of lamivudine

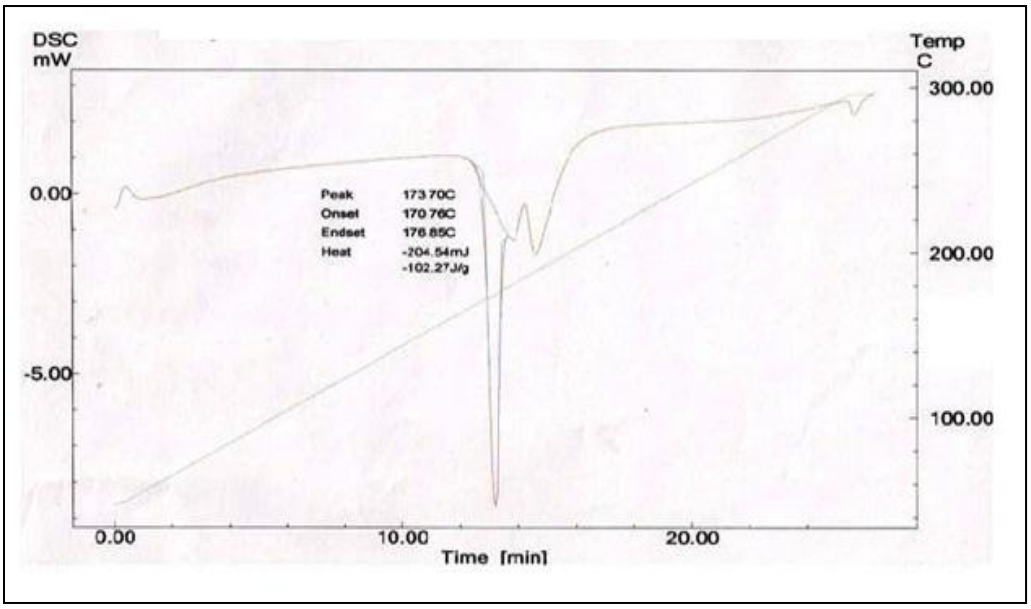



**Figure 8.10:** DSC thermal analysis of lamivudine + HPMC K4M

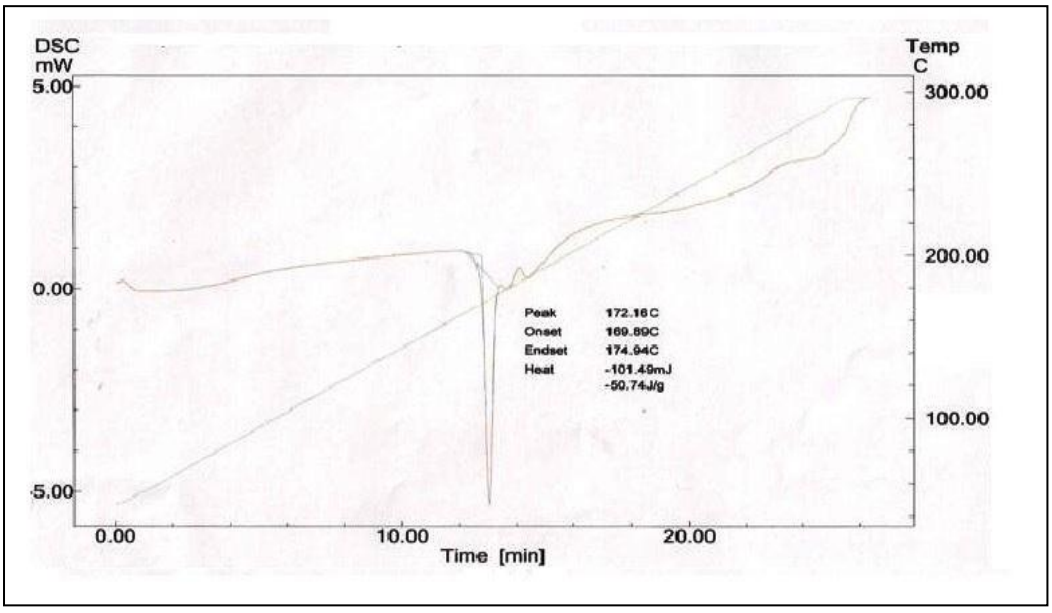



**Figure 8.11:** DSC thermal analysis of lamivudine + methyl cellulose

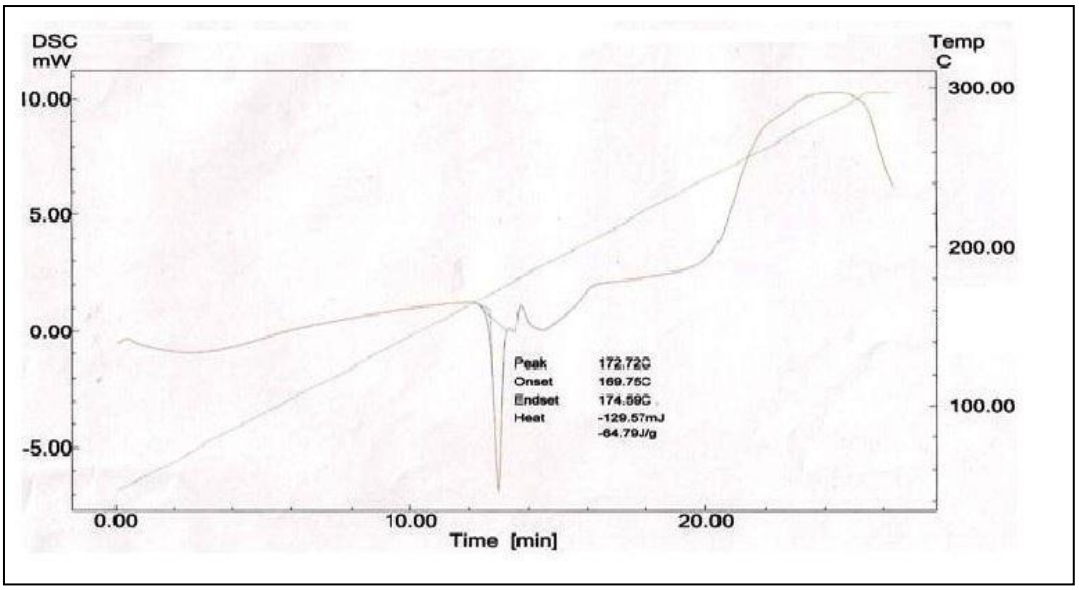



**Figure 8.12:** DSC thermal analysis of lamivudine + ethyl cellulose

According to Figures 8.9 to 8.12 and Table 8.9, DSC thermogram showed that there was no major difference in onset temperature, end set temperature and peak temperature when compared with pure drug thermogram. Therefore it could indicate that there was no incompatibility between drug and different polymers.

**Table 8.9:** DSC thermogram parameters of lamivudine with various polymers

| S. No. | DSC thermogram | Onset temperature (°C) | Peak temperature (°C) | End set temperature (°C) |
|---|---|---|---|---|
| 1 | Lamivudine | 172.24 | 174.17 | 180.30 |
| 2 | Lamivudine + HPMC K4M | 170.70 | 173.70 | 176.85 |
| 3 | Lamivudine + Methylcellulose | 169.59 | 172.16 | 174.04 |
| 4 | Lamivudine + Ethylcellulose | 169.75 | 172.72 | 174.59 |

### 8.2. Evaluation of powder blends:

The blended powders of different formulations were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and Hausner ratio. The results of these evaluations were as follows: -

### 8.2.1. Angle of repose:

Angle of repose ranged from 21.48°± 0.17 to 23.93°± 0.77. The results were found to be below 25° and hence the blend was found to have excellent flowability. (Table No. 8.10).

### 8.2.2. Loose bulk density and tapped bulk density:

Bulk and tapped densities are used for the measurement of Compressibility index. The LBD and TBD ranged from 0.455 ± 0.00 to 0.500 ± 0.00 g/ml; and 0.526 ± 0.00 to 0.556 ± 0.00 g/ml respectively. (Table No. 8.10).

**Table 8.10: Flow characteristics of powder blends**

| Formulation code | Angle of repose (°)* | Loose bulk density (g/ml)* | Tapped bulk density (g/ml)* | Hausner ratio* | Carr's index (%)* |
|---|---|---|---|---|---|
| **LF1** | 22.19±0.98 | 0.455±0.00 | 0.526±0.00 | 1.16±0.00 | 13.636±0.00 |
| **LF2** | 21.48±0.17 | 0.500±0.00 | 0.556±0.00 | 1.11±0.00 | 10.000±0.00 |
| **LF3** | 22.36±0.98 | 0.500±0.00 | 0.556±0.00 | 1.11±0.00 | 10.000±0.00 |
| **LF4** | 23.44±0.73 | 0.455±0.00 | 0.526±0.00 | 1.16±0.00 | 13.636±0.00 |
| **LF5** | 23.05±0.19 | 0.476±0.00 | 0.556±0.00 | 1.17±0.00 | 14.286±0.00 |
| **LF6** | 22.30±0.17 | 0.455±0.00 | 0.526±0.00 | 1.16±0.00 | 13.636±0.00 |
| **LF7** | 23.93±0.77 | 0.476±0.00 | 0.556±0.00 | 1.17±0.00 | 14.286±0.00 |
| **LF8** | 23.20±0.61 | 0.455±0.00 | 0.526±0.00 | 1.16±0.00 | 13.636±0.00 |
| **LF9** | 22.49±0.36 | 0.455±0.00 | 0.526±0.00 | 1.16±0.00 | 13.636±0.00 |

*All the values were expressed as mean± SD, n=3

**8.2.3. Compressibility index (Carr's index):**

The compressibility index (%) ranged from 10.000 ± 0.00 to 14.286 ± 0.00 (Table No.8.10). The blend was found to have excellent flowing property as the result were found to be below 15%.

**8.2.4. Hausner ratio:**

The Hausner ratio ranged from 1.11 ± 0.00 to 1.17 ± 0.00, (Table No.8.10). The result indicates the free flowing properties of the powders.

**8.3. Evaluation of sustained release matrix tablets:**

**8.3.1. Appearance:**

Surface nature of tablets was observed visually and it was concluded they did not show any defects such as capping, chipping and lamination.

**8.3.2. Physico-chemical characteristics:**

The physical characteristics of lamivudine matrix tablets (LF1 toLF9) such as thickness, diameter, hardness, friability, weight variation and drug content were determined and the results were shown in table 8.11.

**8.3.2.1. Dimension (Thickness and Diameter):**

The size (diameter) of the tablets was found to be in the range from 11.17±0.01 mm to 11.2 ± 0.01 and thickness ranged between 4.46 ± 0.05 to 4.55 ± 0.07 mm.

**8.3.2.2. Tablet hardness:**

The hardness of tablets was found to be in the range from 7.35 ± 0.67 kg/cm$^2$ to 8.10 ± 0.39 kg/cm$^2$. This indicates good mechanical strength of tablet.

**8.3.2.3. Percent friability:**

Percentage friability of all the formulations was found to be in the range from 0.050 to 0.150 %. This indicates good handling property of the prepared matrix tablet.

**Table 8.11:** Physico-chemical parameters of lamivudine matrix tablets

| F. Code | Dimension | | Hardness ($kg/cm^2$)* | Friability (%) | Weight variation (mg) | Drug content (%w/w)** |
|---|---|---|---|---|---|---|
| | Diameter (mm)* | Thickness (mm)* | | | | |
| **LF1** | 11.20±0.01 | 4.55±0.07 | 8.05±0.44 | 0.150 | 400.40±1.50 | 99.87±0.28 |
| **LF2** | 11.19±0.02 | 4.46±0.07 | 7.95±0.37 | 0.099 | 402.15±2.94 | 98.48±0.52 |
| **LF3** | 11.20±0.01 | 4.50±0.07 | 8.10±0.39 | 0.050 | 400.90±2.73 | 99.11±0.53 |
| **LF4** | 11.19±0.01 | 4.46±0.05 | 7.75±0.42 | 0.075 | 401.25±3.57 | 99.45±0.92 |
| **LF5** | 11.17±0.01 | 4.49±0.06 | 8.05±0.44 | 0.124 | 402.20±3.61 | 100.08±0.45 |
| **LF6** | 11.17±0.04 | 4.52±0.04 | 8.00±0.58 | 0.100 | 401.75±2.22 | 99.40±0.31 |
| **LF7** | 11.19±0.01 | 4.54±0.10 | 7.55±0.55 | 0.087 | 400.80±3.24 | 100.15±0.43 |
| **LF8** | 11.19±0.01 | 4.49±0.07 | 7.35±0.67 | 0.050 | 403.05±3.12 | 100.90±0.45 |
| **LF9** | 11.18±0.01 | 4.51±0.06 | 8.05±0.44 | 0.100 | 402.95±2.28 | 98.93±0.86 |

*All the values were expressed as mean ± SD, n=10; ******All the values were expressed as mean ± SD, n=3.

**8.3.2.4. Weight variation:**

A tablet is designed to contain a specific amount of drug. When the average weight of the tablet is 400 mg, the pharmacopoeial limit for percentage deviation is ± 5%. The percentage deviation from average tablet weight for all the tablet was found to be within the specified limits and hence all formulations complied with the test for weight variation according to the pharmacopoeial specifications IP 2007.

**8.3.2.5. Drug content:**

The drug content of all the formulation was found to be in the range from 98.48 ± 0.52 to 100.90 ± 0.45 % w/w, which was within the specified limit as per IP 2007.

### 8.3.3. *In vitro* dissolution studies:

**Table 8.12:** Dissolution profile of formulation LF1

| Time (hours) | Percentage drug released* | Amount (mg) | % DE | MDT |
|---|---|---|---|---|
| 0 | 0.00±0.00 | 0.00 | 0.00 | 0.00 |
| 1 | 14.38±0.58 | 28.76 | 7.24 | 0.50 |
| 2 | 29.43±0.64 | 58.86 | 14.61 | 1.01 |
| 3 | 33.56±0.53 | 67.11 | 20.18 | 1.18 |
| 4 | 37.55±1.31 | 75.10 | 23.98 | 1.45 |
| 5 | 49.49±1.35 | 98.98 | 27.90 | 2.19 |
| 6 | 54.33±0.92 | 108.70 | 31.93 | 2.48 |
| 7 | 64.69±0.82 | 129.40 | 35.89 | 3.12 |
| 8 | 69.65±0.58 | 139.30 | 39.81 | 3.43 |
| 9 | 74.90±1.06 | 149.80 | 43.43 | 3.79 |
| 10 | 78.44±0.92 | 156.90 | 46.78 | 4.06 |
| 11 | 86.73±0.69 | 173.50 | 50.03 | 4.62 |
| 12 | 92.56±1.85 | 185.10 | 53.30 | 5.07 |

*****All values were expressed as mean ±SD, n=3.

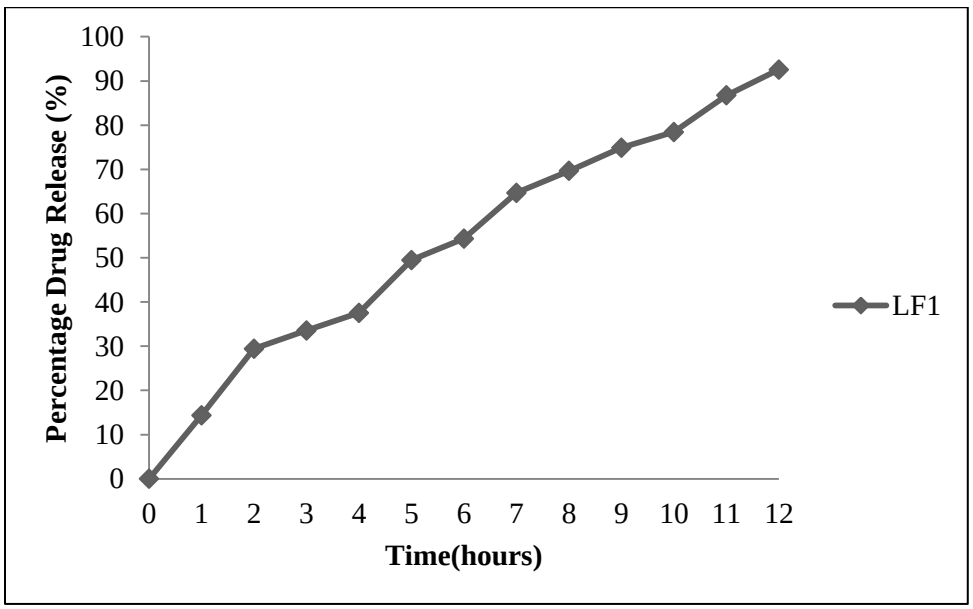



**Figure 8.13:** *In vitro* drug release profile of formulation LF1

**Table 8.13:** Dissolution profile of formulation LF2

| Time (hours) | Percentage drug released* | Amount (mg) | % DE | MDT |
|---|---|---|---|---|
| **0** | 0.00±0.00 | 0.00 | 0.00 | 0.00 |
| **1** | 12.69±0.69 | 25.38 | 6.33 | 0.50 |
| **2** | 25.17±0.69 | 50.35 | 12.63 | 1.00 |
| **3** | 29.45±0.82 | 58.9 | 17.53 | 1.21 |
| **4** | 36.24±0.63 | 72.49 | 21.38 | 1.65 |
| **5** | 42.96±0.86 | 85.93 | 25.04 | 2.09 |
| **6** | 48.45±0.88 | 96.91 | 28.49 | 2.47 |
| **7** | 53.98±0.82 | 108.00 | 31.75 | 2.89 |
| **8** | 58.17±1.05 | 116.30 | 34.81 | 3.23 |
| **9** | 67.34±0.82 | 134.70 | 37.95 | 3.95 |
| **10** | 78.63±0.47 | 157.30 | 41.48 | 4.74 |
| **11** | 81.05±0.52 | 162.10 | 44.98 | 4.90 |
| **12** | 89.57±0.63 | 179.10 | 48.33 | 5.51 |

*****All values were expressed as mean ±SD, n=3.

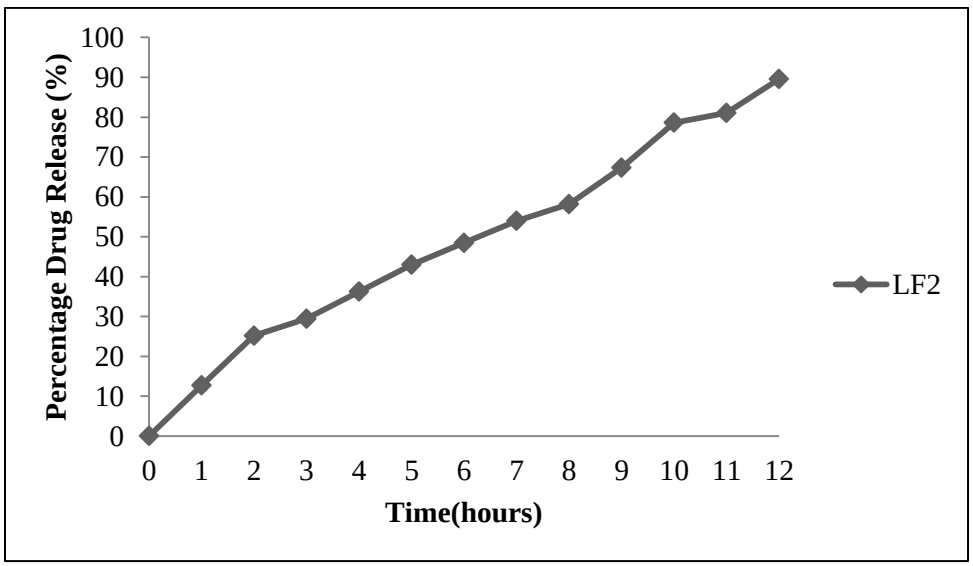



**Figure 8.14:** *In vitro* drug release profile of formulation LF2

**Table 8.14:** Dissolution profile of formulation LF3

| Time (hours) | Percentage drug released* | Amount (mg) | % DE | MDT |
|---|---|---|---|---|
| **0** | 0.00±0.00 | 0.00 | 0.00 | 0.00 |
| **1** | 11.25±0.39 | 22.51 | 5.77 | 0.50 |
| **2** | 20.43±0.50 | 40.86 | 10.83 | 0.93 |
| **3** | 26.57±0.86 | 53.14 | 15.00 | 1.30 |
| **4** | 32.41±0.87 | 64.81 | 18.60 | 1.70 |
| **5** | 37.59±0.81 | 75.18 | 21.88 | 2.09 |
| **6** | 43.42±0.70 | 86.85 | 24.99 | 2.56 |
| **7** | 47.57±0.69 | 95.14 | 27.94 | 2.90 |
| **8** | 49.99±0.47 | 99.98 | 30.56 | 3.12 |
| **9** | 59.28±0.70 | 118.60 | 33.26 | 3.97 |
| **10** | 67.88±1.04 | 135.80 | 36.31 | 4.66 |
| **11** | 72.33±0.59 | 144.70 | 39.40 | 5.03 |
| **12** | 81.28±1.23 | 162.60 | 42.54 | 5.74 |

*****All values were expressed as mean ±SD, n=3.

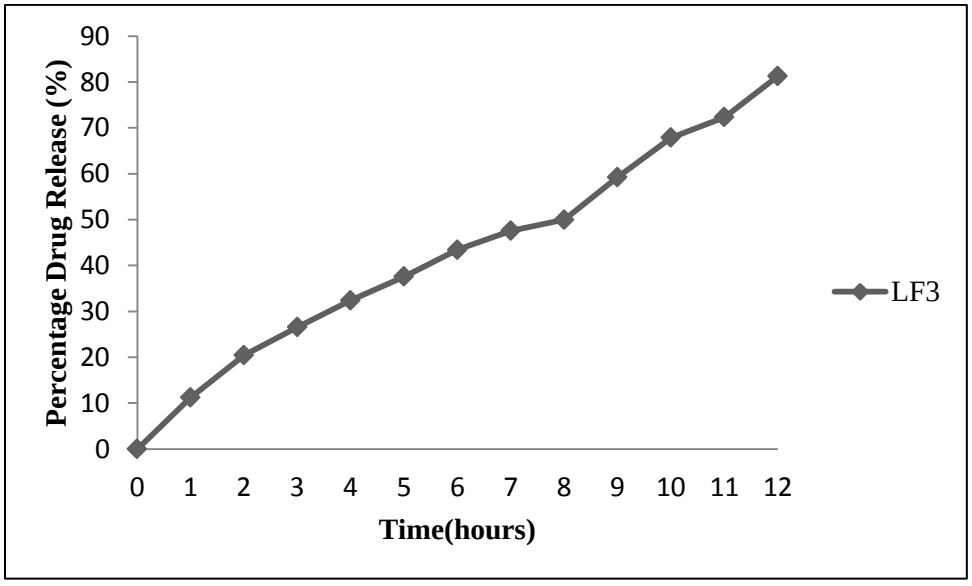



**Figure 8.15:** *In vitro* drug release profile of formulation LF3

**Table 8.15:** Dissolution profile of formulation LF4

| Time (hours) | Percentage drug released* | Amount (mg) | % DE | MDT |
|---|---|---|---|---|
| **0** | 0.00±0.00 | 0.00 | 0.00 | 0.00 |
| **1** | 16.12±0.49 | 32.25 | 8.45 | 0.50 |
| **2** | 31.25±0.67 | 62.50 | 16.25 | 0.96 |
| **3** | 35.25±0.63 | 70.49 | 21.90 | 1.14 |
| **4** | 39.51±0.63 | 79.02 | 25.78 | 1.40 |
| **5** | 47.42±0.82 | 94.83 | 29.34 | 1.92 |
| **6** | 56.21±0.47 | 112.40 | 33.13 | 2.48 |
| **7** | 66.57±0.86 | 133.10 | 37.21 | 3.11 |
| **8** | 71.33±0.76 | 142.70 | 41.23 | 3.41 |
| **9** | 79.63±0.98 | 159.30 | 45.06 | 3.90 |
| **10** | 83.24±0.78 | 166.50 | 48.71 | 4.17 |
| **11** | 89.95±0.92 | 179.90 | 52.16 | 4.61 |
| **12** | 96.63±1.05 | 193.30 | 55.59 | 5.11 |

*****All values were expressed as mean ±SD, n=3.

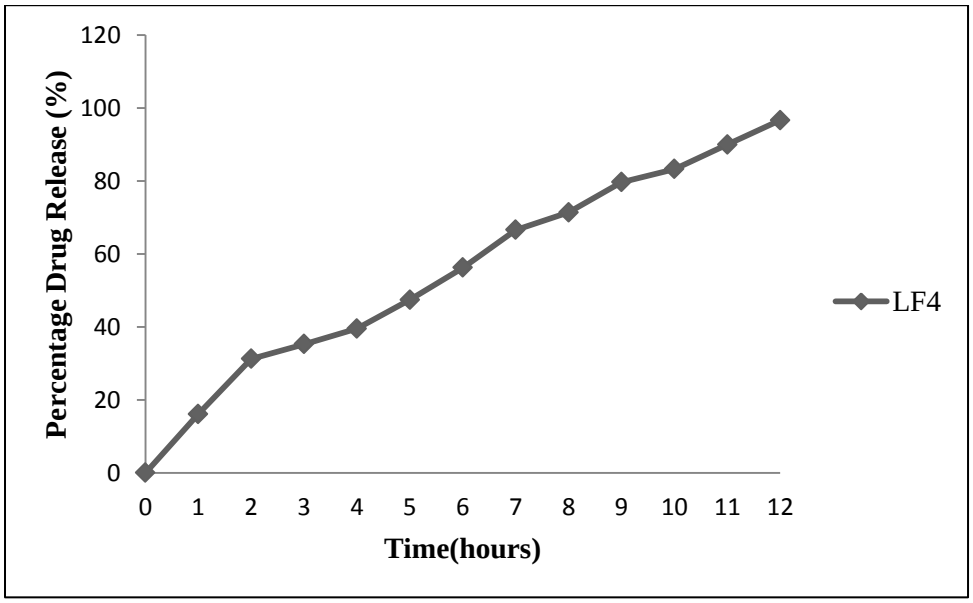



**Figure 8.16:** *In vitro* drug release profile of formulation LF4

**Table 8.16:** Dissolution profile of formulation LF5

| Time (hours) | Percentage drug released* | Amount (mg) | % DE | MDT |
|---|---|---|---|---|
| **0** | 0.00±0.00 | 0.00 | 0.00 | 0.00 |
| **1** | 14.18±0.42 | 28.35 | 7.34 | 0.50 |
| **2** | 28.45±0.46 | 56.91 | 14.43 | 0.98 |
| **3** | 32.14±0.77 | 64.27 | 19.69 | 1.16 |
| **4** | 37.86±0.63 | 75.71 | 23.49 | 1.51 |
| **5** | 45.69±0.47 | 91.38 | 27.11 | 2.02 |
| **6** | 51.68±0.98 | 103.40 | 30.70 | 2.43 |
| **7** | 62.77±0.70 | 125.50 | 34.49 | 3.16 |
| **8** | 67.34±0.69 | 134.70 | 38.33 | 3.46 |
| **9** | 74.60±0.78 | 149.20 | 41.97 | 3.94 |
| **10** | 80.59±0.81 | 161.20 | 45.55 | 4.36 |
| **11** | 86.23±0.54 | 172.50 | 49.00 | 4.76 |
| **12** | 93.52±0.63 | 187.00 | 52.42 | 5.29 |

*****All values were expressed as mean ±SD, n=3.

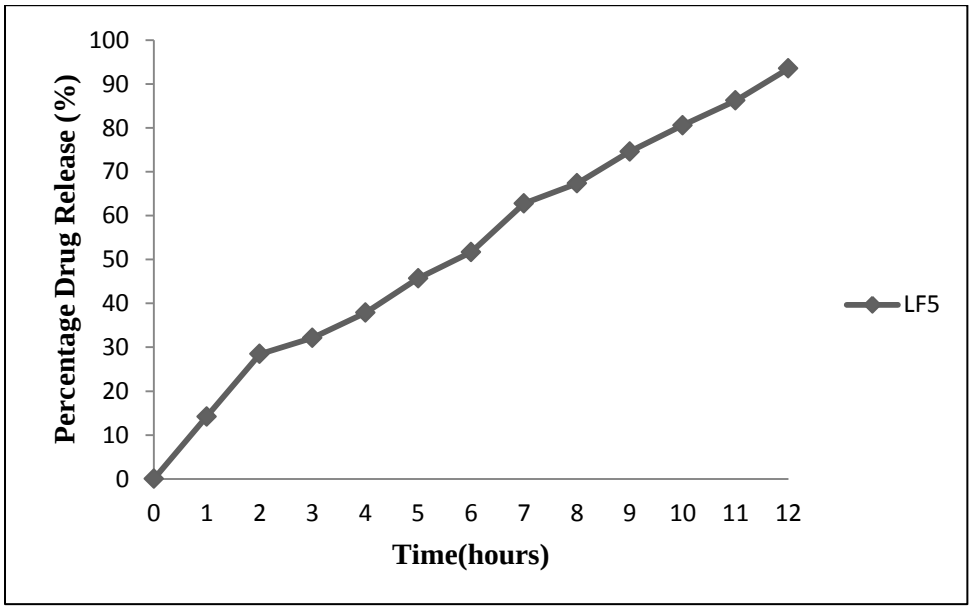



**Figure 8.17:** *In vitro* drug release profile of formulation LF5

**Table 8.17:** Dissolution profile of formulation LF6

| Time (hours) | Percentage drug released* | Amount (mg) | % DE | MDT |
|---|---|---|---|---|
| **0** | 0.00±0.00 | 0.00 | 0.00 | 0.00 |
| **1** | 13.05±0.42 | 25.38 | 6.78 | 0.50 |
| **2** | 25.84±0.41 | 50.35 | 13.14 | 0.97 |
| **3** | 29.68±0.70 | 58.90 | 17.92 | 1.18 |
| **4** | 35.44±0.58 | 72.49 | 21.58 | 1.57 |
| **5** | 44.08±0.58 | 85.93 | 25.22 | 2.14 |
| **6** | 48.53±0.42 | 96.91 | 28.71 | 2.43 |
| **7** | 55.75±1.11 | 108.00 | 32.01 | 2.95 |
| **8** | 61.62±1.15 | 116.30 | 35.30 | 3.40 |
| **9** | 66.77±0.40 | 134.70 | 38.48 | 3.79 |
| **10** | 76.98±0.83 | 157.30 | 41.80 | 4.57 |
| **11** | 82.70±0.59 | 162.10 | 45.26 | 4.97 |
| **12** | 89.95±0.82 | 179.10 | 48.67 | 5.49 |

*****All values were expressed as mean ±SD, n=3.

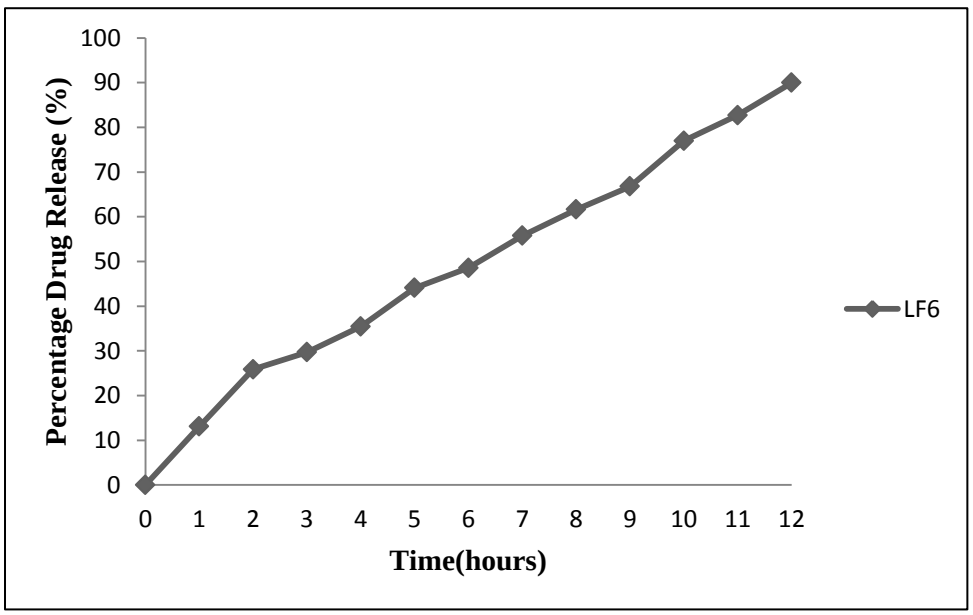



**Figure 8.18:** *In vitro* drug release profile of formulation LF6

**Table 8.18:** Dissolution profile of formulation LF7

| Time (hours) | Percentage drug released* | Amount (mg) | % DE | MDT |
|---|---|---|---|---|
| **0** | 0.00±0.00 | 0.00 | 0.00 | 0.00 |
| **1** | 14.59±0.77 | 29.17 | 7.29 | 0.50 |
| **2** | 29.79±0.85 | 59.58 | 14.68 | 1.01 |
| **3** | 33.98±0.52 | 67.96 | 20.33 | 1.19 |
| **4** | 38.55±0.82 | 77.10 | 24.30 | 1.49 |
| **5** | 46.57±0.64 | 93.14 | 27.98 | 2.00 |
| **6** | 55.67±0.76 | 111.30 | 31.85 | 2.57 |
| **7** | 65.46±1.10 | 130.90 | 35.96 | 3.15 |
| **8** | 70.22±0.29 | 140.40 | 39.96 | 3.46 |
| **9** | 76.44±1.16 | 152.90 | 43.68 | 3.86 |
| **10** | 82.39±0.23 | 164.80 | 47.25 | 4.25 |
| **11** | 88.65±0.75 | 177.30 | 50.72 | 4.71 |
| **12** | 94.71±0.81 | 189.40 | 54.14 | 5.15 |

*****All values were expressed as mean ±SD, n=3.

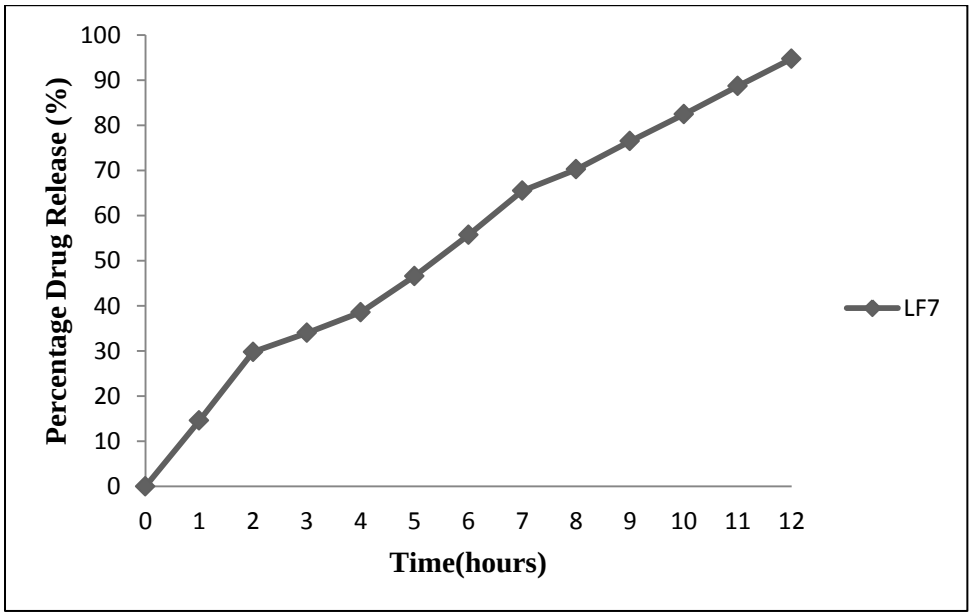



**Figure 8.19:** *In vitro* drug release profile of formulation LF7

**Table 8.19:** Dissolution profile of formulation LF8

| Time (hours) | Percentage drug released* | Amount (mg) | % DE | MDT |
|---|---|---|---|---|
| **0** | 0.00±0.00 | 0.00 | 0.00 | 0.00 |
| **1** | 13.38±0.31 | 26.76 | 6.78 | 0.50 |
| **2** | 26.89±0.74 | 53.78 | 13.47 | 0.99 |
| **3** | 32.29±0.92 | 64.58 | 18.83 | 1.26 |
| **4** | 37.09±0.44 | 74.18 | 22.79 | 1.53 |
| **5** | 44.58±0.75 | 89.15 | 26.40 | 2.04 |
| **6** | 50.26±0.92 | 100.50 | 29.92 | 2.44 |
| **7** | 57.36±0.52 | 114.70 | 33.34 | 2.93 |
| **8** | 62.66±0.58 | 125.30 | 36.65 | 3.30 |
| **9** | 69.18±0.98 | 138.40 | 39.88 | 3.80 |
| **10** | 79.32±1.11 | 158.60 | 43.31 | 4.54 |
| **11** | 85.88±0.58 | 171.80 | 46.88 | 4.98 |
| **12** | 91.26±0.98 | 182.50 | 50.36 | 5.40 |

*****All values were expressed as mean ±SD, n=3.

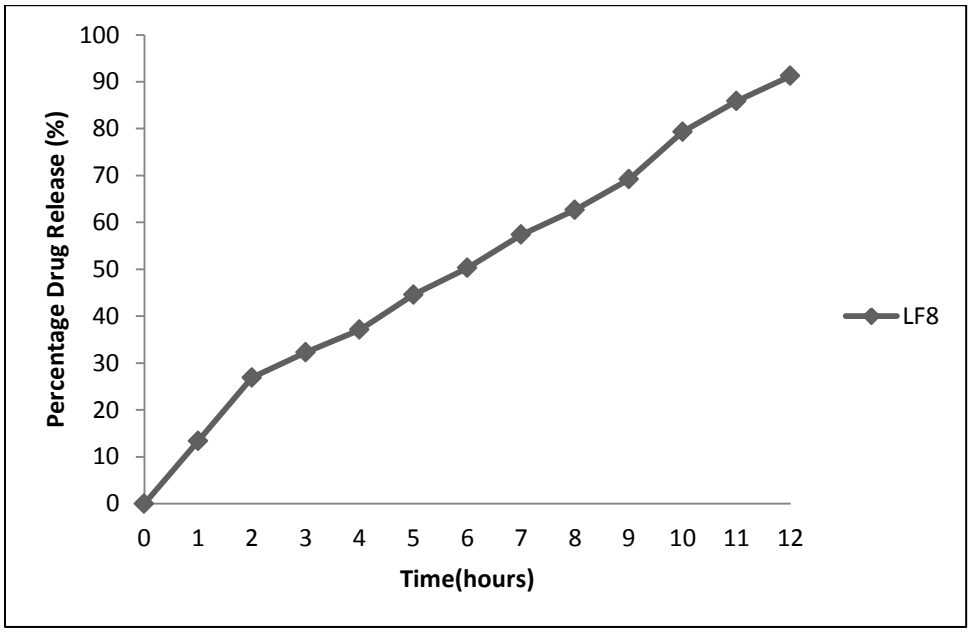



**Figure 8.20:** *In vitro* drug release profile of formulation LF8

**Table 8.20:** Dissolution profile of formulation LF9

| Time (hours) | Percentage drug released* | Amount (mg) | % DE | MDT |
|---|---|---|---|---|
| **0** | 0.00±0.00 | 0.00 | 0.00 | 0.00 |
| **1** | 12.15±0.15 | 24.30 | 6.18 | 0.50 |
| **2** | 24.92±0.50 | 49.83 | 12.38 | 1.00 |
| **3** | 28.41±1.05 | 56.83 | 17.11 | 1.19 |
| **4** | 34.52±0.69 | 69.03 | 20.69 | 1.60 |
| **5** | 43.42±0.82 | 86.85 | 24.37 | 2.21 |
| **6** | 47.69±0.75 | 95.37 | 27.93 | 2.49 |
| **7** | 54.75±1.02 | 109.50 | 31.24 | 2.99 |
| **8** | 60.43±0.78 | 120.90 | 34.51 | 3.42 |
| **9** | 64.27±0.59 | 128.50 | 37.60 | 3.73 |
| **10** | 75.48±0.58 | 151.00 | 40.82 | 4.60 |
| **11** | 81.66±0.69 | 163.30 | 44.26 | 5.03 |
| **12** | 86.92±0.70 | 173.80 | 47.60 | 5.44 |

*****All values were expressed as mean ±SD, n=3.

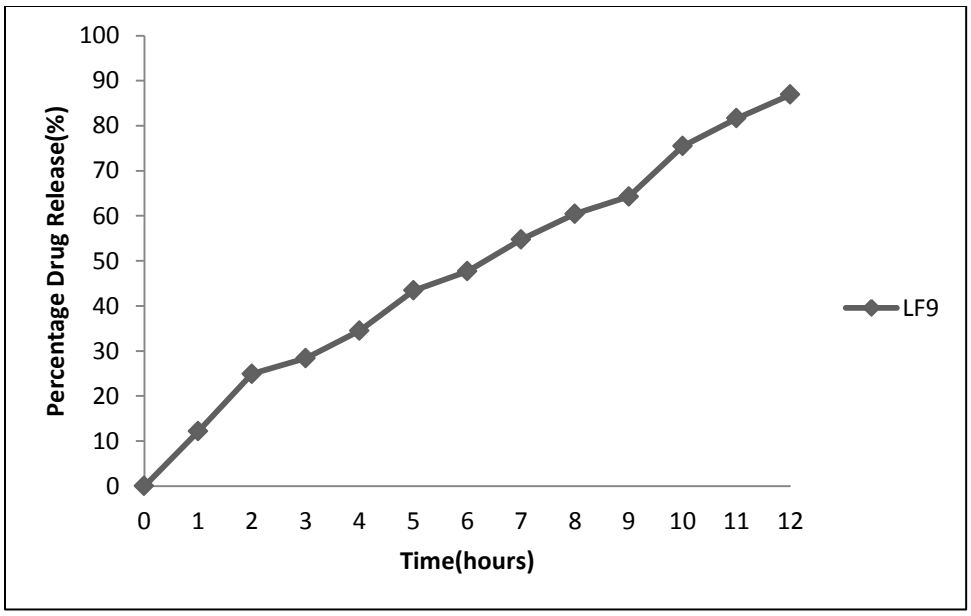



**Figure 8.21:** *In vitro* drug release profile of formulation LF9

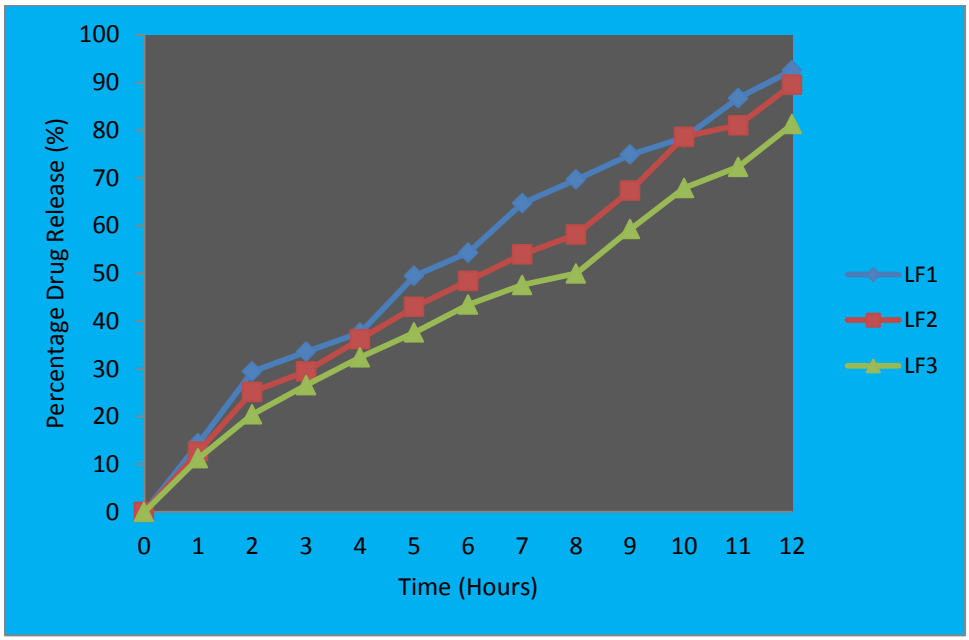



**Figure 8.22:** *In vitro* drug release profile of formulations containing HPMC K4M polymer.

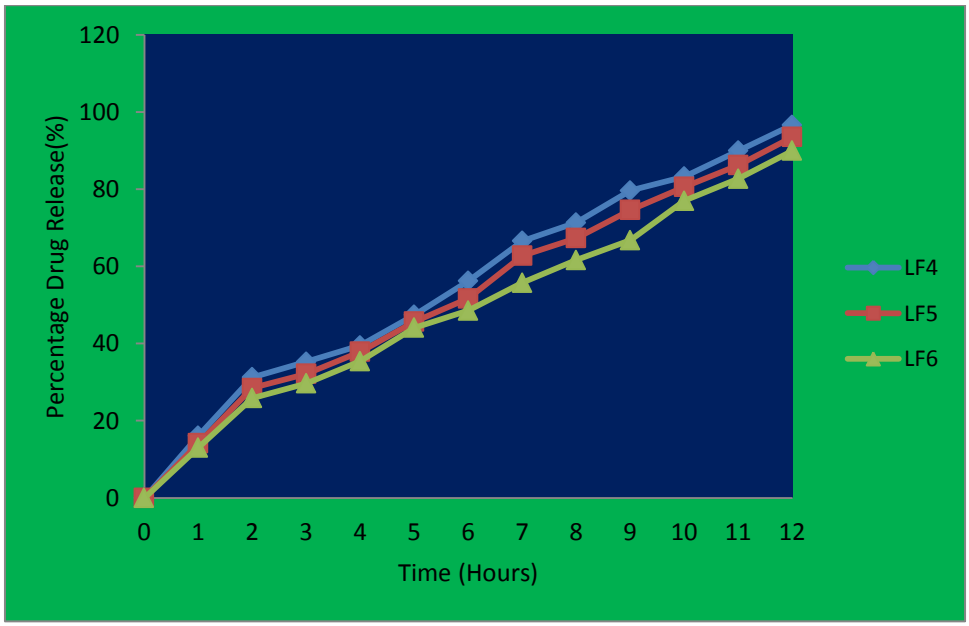



**Figure 8.23:** *In vitro* drug release profile of formulations containing methylcellulose polymer.

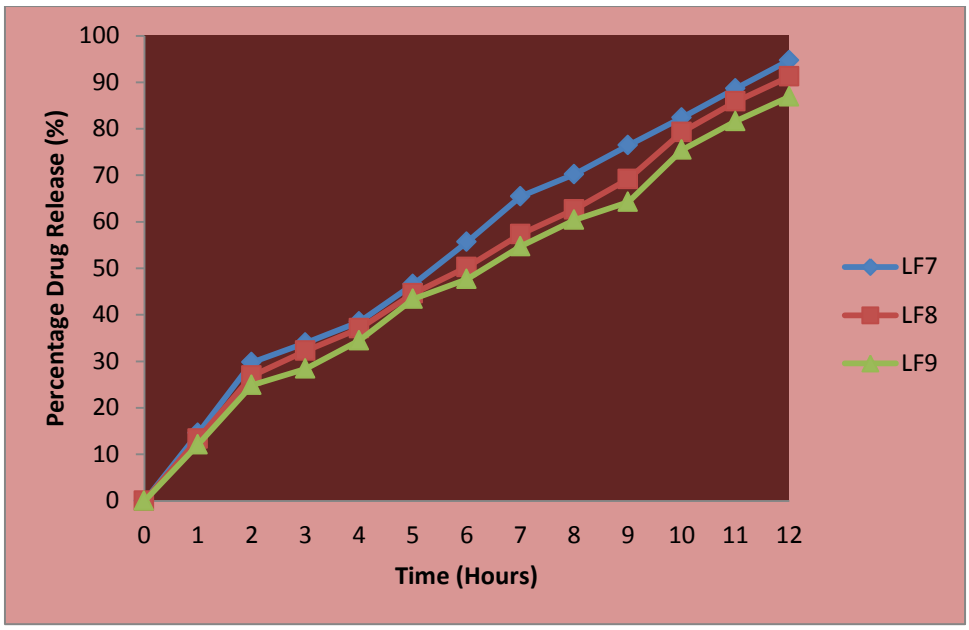



**Figure 8.24:** *In vitro* Drug Release profile of formulations containing ethylcellulose polymer.

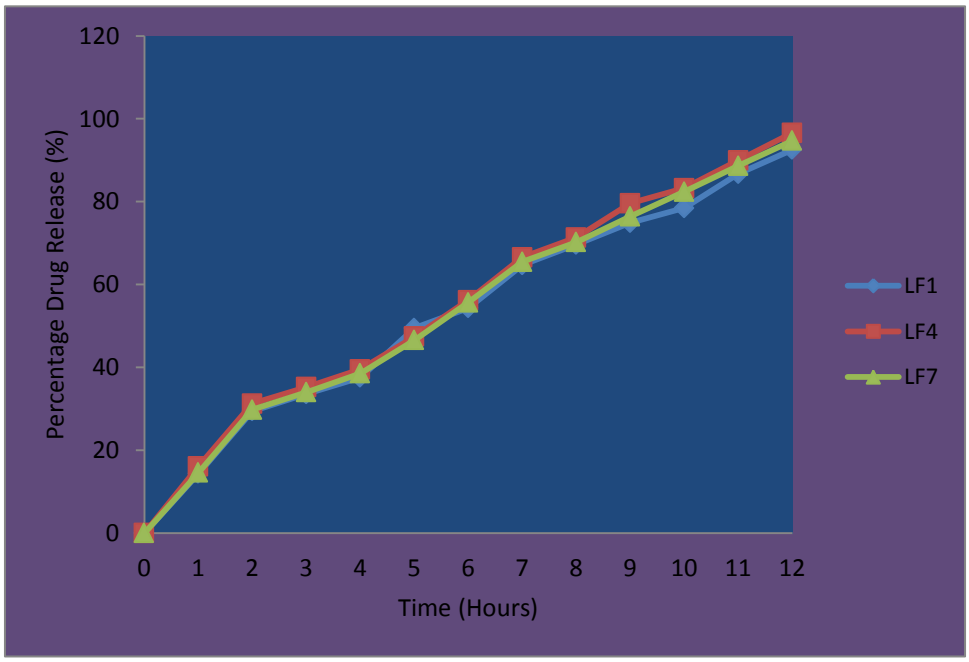



**Figure 8.25:** *In vitro* drug release profile for different polymers at 10% concentration.

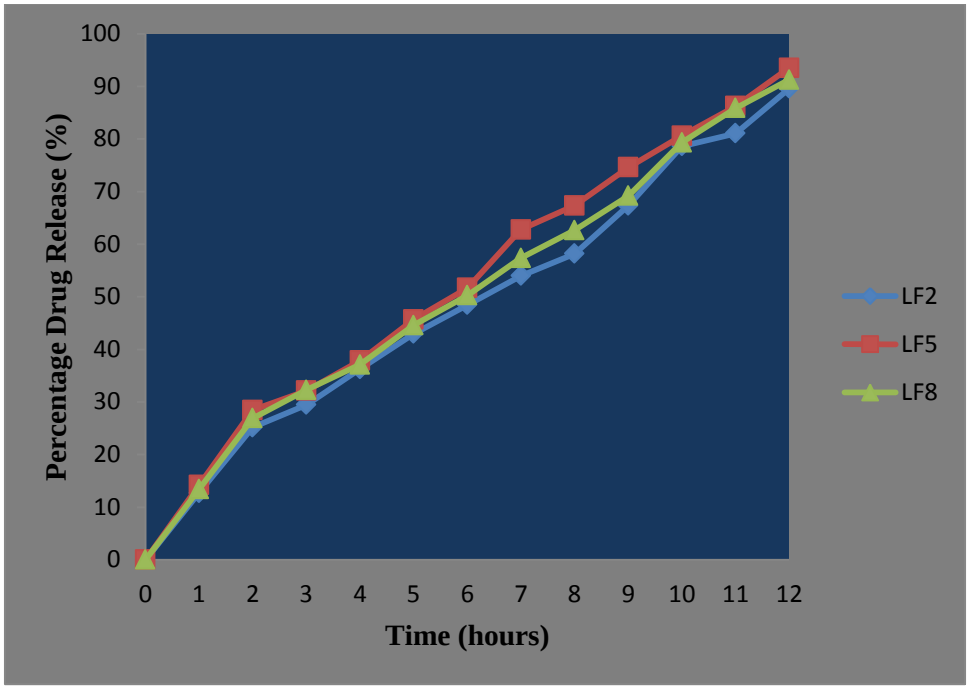



**Figure 8.26:** *In vitro* drug release profile for different polymers at 20% concentration.

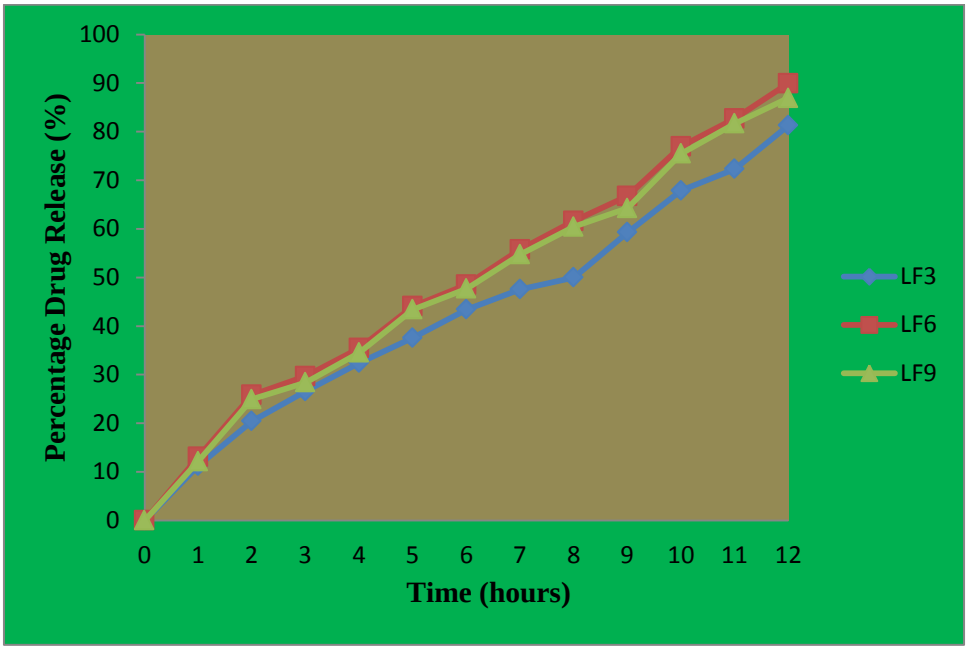



**Figure 8.27:** *In vitro* drug release profile for different polymers at 30% concentration.

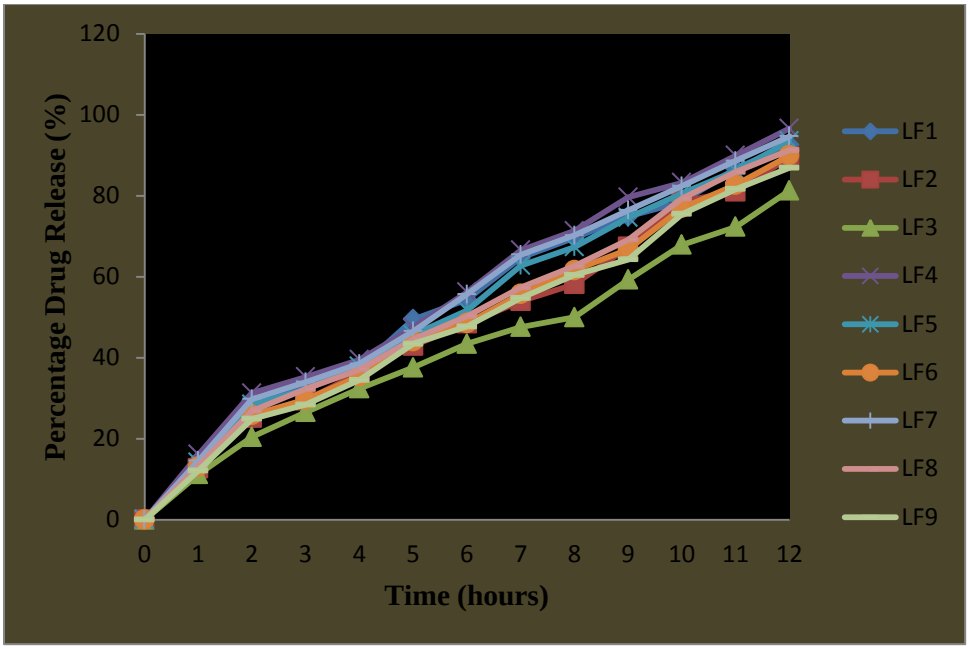



**Figure 8.28:** *In vitro* drug release profile of LF1 to LF9.

**Table 8.21:** Time of *in vitro* drug release for lamivudine $t_{50\%}$ values of LF1 to LF9.

| Formulation code | Time of drug release (hours) ($t_{50\%}$) |
|---|---|
| LF1 | 5.2 |
| LF2 | 6.3 |
| LF3 | 8.0 |
| LF4 | 5.3 |
| LF5 | 5.8 |
| LF6 | 6.2 |
| LF7 | 5.3 |
| LF8 | 6.0 |
| LF9 | 6.4 |

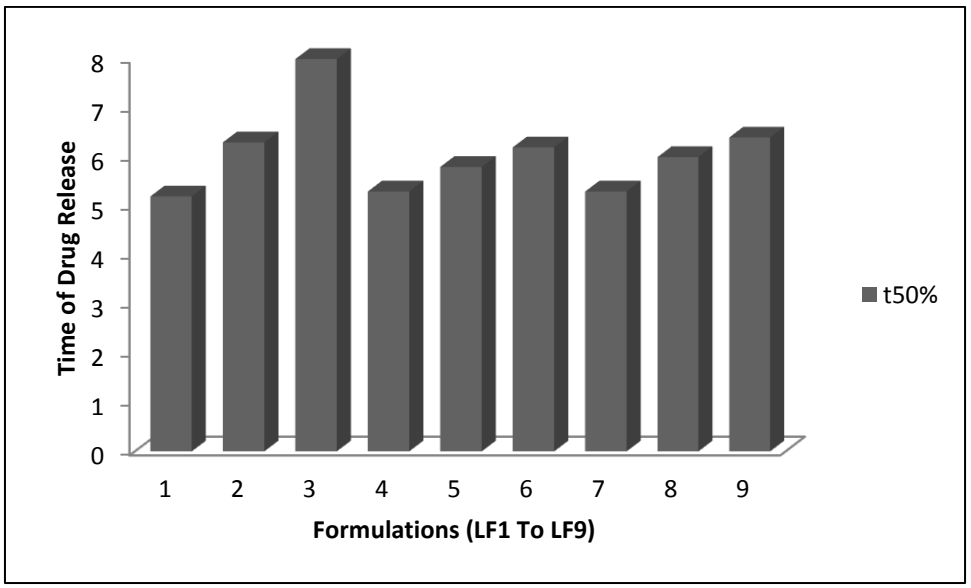



**Figure 8.29:** *In vitro* drug release for $t_{50\%}$ values of LF1 to LF9.

Lamivudine drug was soluble in phosphate buffers and its release from the matrix was largely dependent on the polymer swelling, drug diffusion and matrix erosion. The concentration of polymer in the matrix tablet was a key factor in sustaining the drug release.

Various sustained release formulations were formulated with HPMC K4M, methyl cellulose and ethyl cellulose polymer alone; polyvinyl pyrrolidone as binder and microcrystalline cellulose was used as diluents.

The variation in drug release was due to different types of polymers and different concentrations of polymer in all the nine formulations. It is expected that the developed formulations should have the following theoretical drug release profile.

The drug released from formulation LF1 to LF3 containing HPMC K4M at three concentration levels of 10%, 20%, 30% were found to be 92.56 ± 1.85, 89.57 ± 0.63, and 81.28 ± 1.23% for lamivudine respectively at the end of 12 hours. It was shown in Tables (8.12, 8.13 and 8.14).

The drug released from formulation LF4 to LF6 containing methyl cellulose at three concentration levels of 10%, 20%, 30% were found to be 96.63 ± 1.05, 93.52 ± 0.63 and 89.95 ± 0.82% for lamivudine respectively at the end of 12 hours . It was shown in Tables (8.15, 8.16 and 8.17).

The drug released from formulation LF7 to LF9 containing ethyl cellulose at three concentration levels of 10%, 20%, 30% were found to be 94.71 ± 0.81, 91.26 ± 0.98 and 86.92 ± 0.70% for lamivudine respectively at the end of 12 hours. It was shown in Tables (8.18, 8.19 and 8.20).

The drug release rate from HPMC K4M matrix was found to be less as compared to methyl cellulose and ethyl cellulose; it was shown in Figure 8.22. This might be due to slow hydration of matrix and its property to form a thick gel layer, it's due to slow erosion of matrix and its property which retard the drug release from the tablet for long duration.

The overall release rate of lamivudine from methylcellulose and ethylcellulose matrices are significantly higher than that from HPMC K4M matrices were shown in Figure 8.28 and which is confirmed by smaller MDT (5.11, 5.29, 5.49 and 5.15, 5.40, 5.44) respectively for methylcellulose and ethylcellulose and higher MDT for HPMC K4M matrices. These results are indicating that HPMC K4M has higher drug retarding ability for long duration than ethylcellulose and methylcellulose. HPMC K4M also showed the least %DE while ethylcellulose and methylcellulose also showed the greatest %DE among the tablets with just one of the retarding polymers.

The result of $t_{50\%}$ was shown in Table 8.21 and Figure 8.29, according to the time of drug release values of $t_{50\%}$, the formulation LF3 was selected as the best formulation.

In addition to concentration of polymer, the type and viscosity of polymer also influences drug release. When drug release data obtained from dissolution study of different polymers at 10%, 20% and 30% concentration is plotted against time (Figures 8.25, 8.26 and 8.27) respectively, it was observed that low concentration of polymer induces more drug release. High concentration of polymer should be retarding the drug release for longer period of time.

The comparative effect of the drug and polymers on the release profile from the formulation and comparing the MDT, %DE and $t_{50\%}$ of tablets showed the formulation containing HPMC K4M release the drug for longer period of time compared to ethylcellulose and methylcellulose. From the above study, the formulation LF3 was concluded as the best formulation among all the nine formulation of this series. Hence the formulation LF3 was selected for further stability study.

### 8.3.4. Kinetics of *in vitro* drug release:

In order to investigate the release mechanism, the data were fitted to models representing first order, zero order, higuchi and korsmeyer- Peppas. The linear regression analysis shown as 'r' values in Table 8.22, demonstrated that all the formulated tablets follows korsmeyer- Peppas release kinetics. The result obtained was shown in Figures 8.30 to 8.38.

**Table 8.22: Different kinetic models for lamivudine matrix tablets (LF1 to LF9)**

| F. Code | Zero order | First order | Higuchi | Korsemeyer- Peppas | | Best fit model |
|---|---|---|---|---|---|---|
| | $R^2$ | $R^2$ | $R^2$ | $R^2$ | n | |
| **LF1** | 0.978 | 0.918 | 0.970 | 0.987 | 0.720 | Peppas |
| **LF2** | 0.988 | 0.895 | 0.950 | 0.989 | 0.749 | Peppas |
| **LF3** | 0.988 | 0.927 | 0.945 | 0.992 | 0.759 | Peppas |
| **LF4** | 0.981 | 0.849 | 0.967 | 0.986 | 0.698 | Peppas |
| **LF5** | 0.986 | 0.890 | 0.962 | 0.989 | 0.731 | Peppas |
| **LF6** | 0.989 | 0.899 | 0.955 | 0.990 | 0.743 | Peppas |
| **LF7** | 0.983 | 0.888 | 0.967 | 0.987 | 0.726 | Peppas |
| **LF8** | 0.988 | 0.892 | 0.957 | 0.989 | 0.736 | Peppas |
| **LF9** | 0.989 | 0.922 | 0.955 | 0.990 | 0.759 | Peppas |

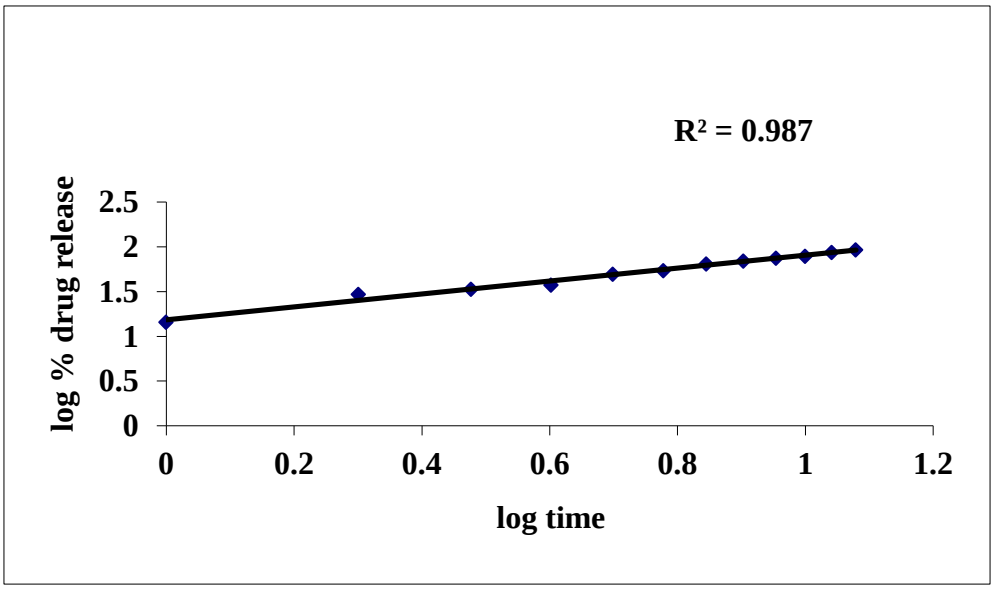



**Figure 8.30:** Best fit model (Peppas) of formulation LF1

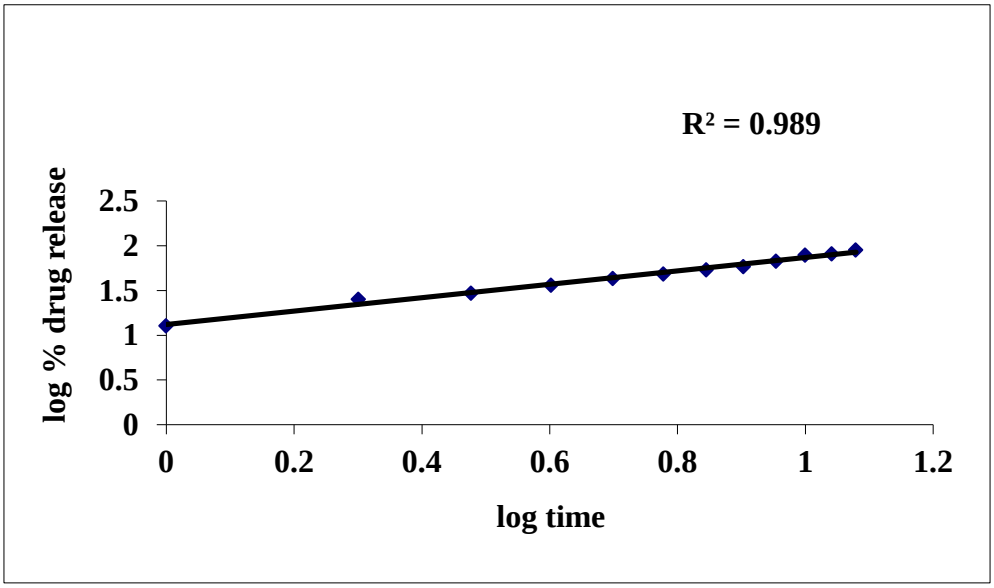



**Figure 8.31:** Best fit model (Peppas) of formulation LF2

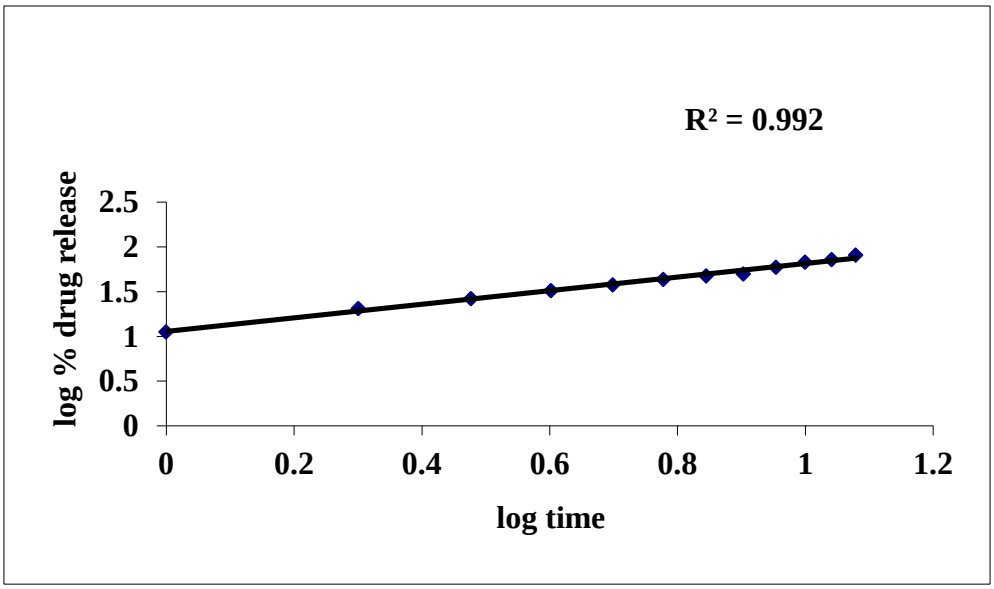



**Figure 8.32:** Best fit model (Peppas) of formulation LF3

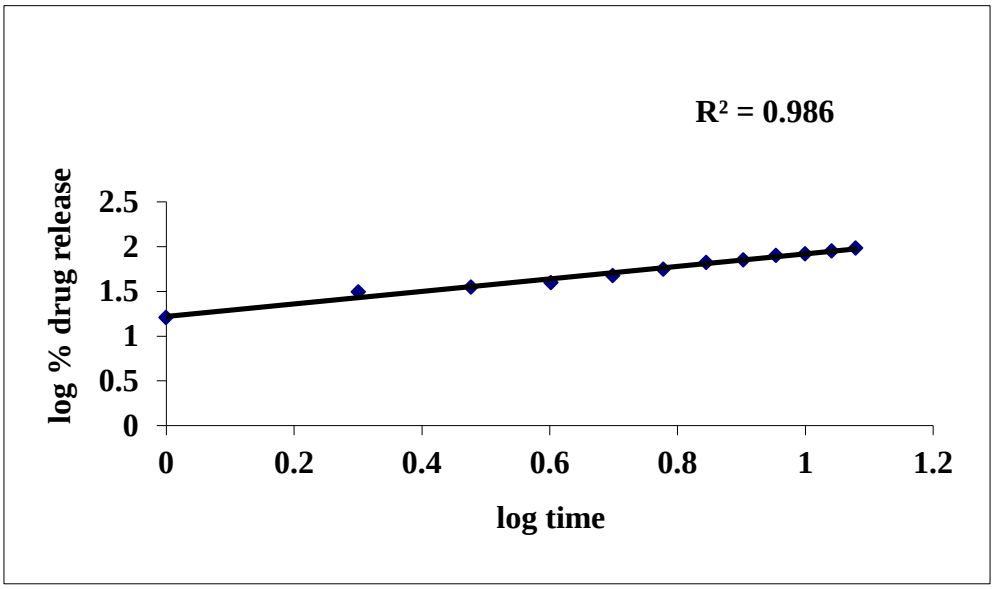



**Figure 8.33:** Best fit model (Peppas) of formulation LF4

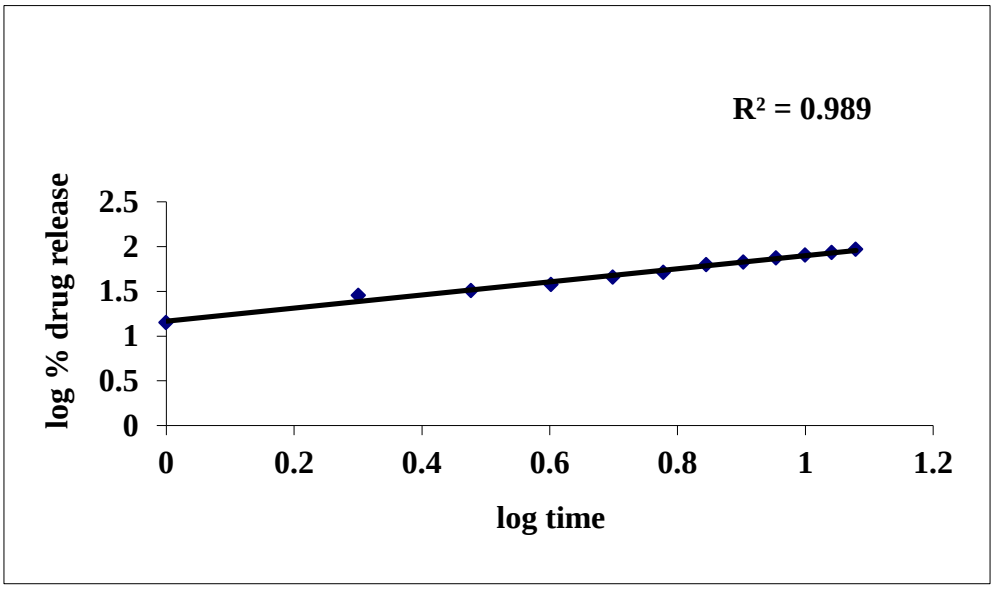



**Figure 8.34:** Best fit model (Peppas) of formulation LF5

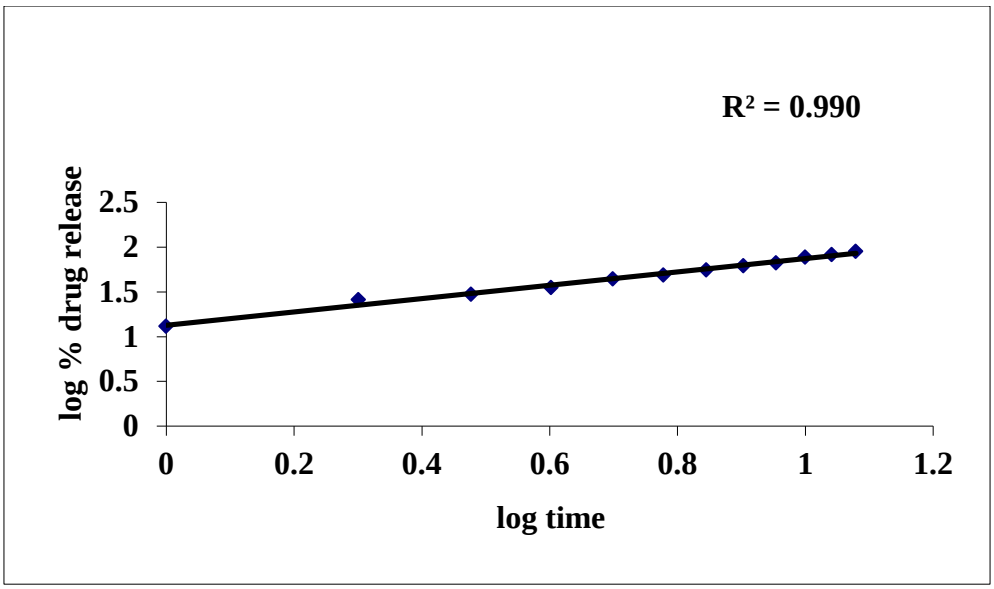



**Figure 8.35:** Best fit model (Peppas) of formulation LF6

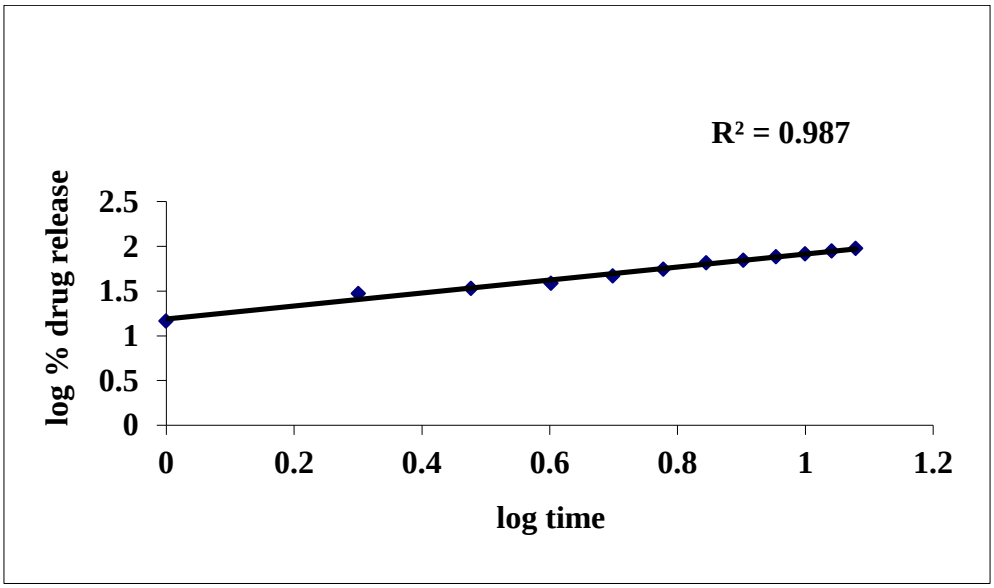



**Figure 8.36:** Best fit model (Peppas) of formulation LF7

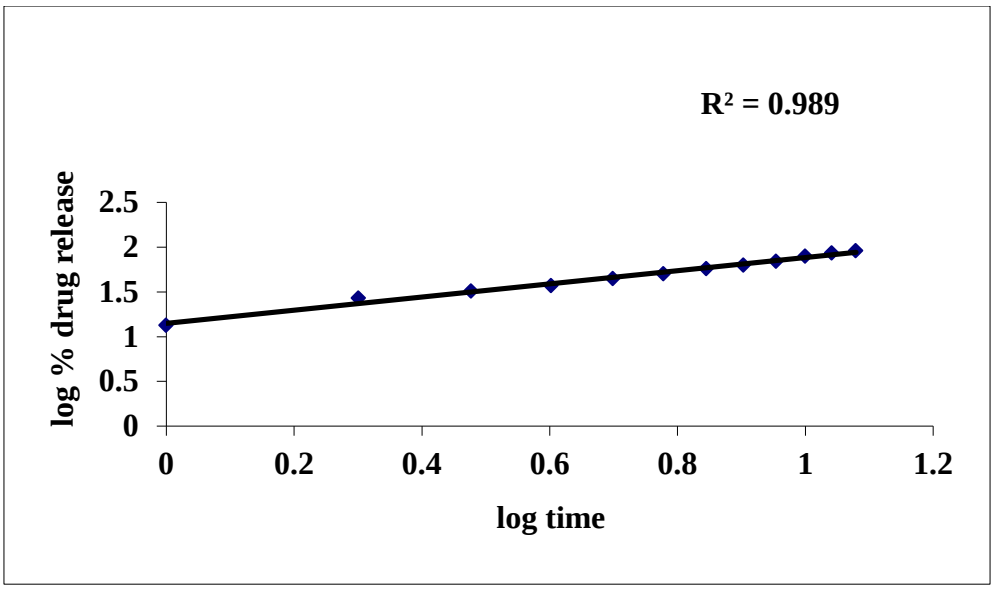



**Figure 8.37:** Best fit model (Peppas) of formulation LF8

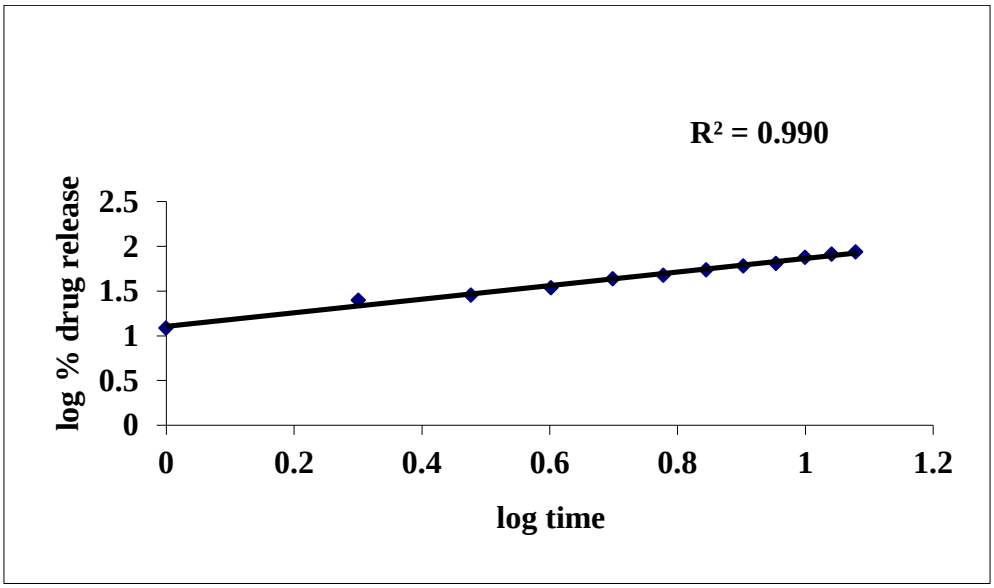



**Figure 8.38:** Best fit model (Peppas) of formulation LF9

Further, to understand the drug release mechanism, the data were fitted to korsmeyer- Peppas exponent equation, when n < 0.45 indicates fickian drug release. For 0.45 < n < 0.89 as anomalous diffusion (non-fickian). In the present study also it

was observed that almost all the formulated tablets followed anomalous diffusion mechanism, which indicates the drug release through diffusion coupled with erosion.

**8.4. Stability study:**

After exposure to accelerated stability conditions the formulation was analyzed for various evaluation parameters; results were shown in Table 8.23 and Figures 8.39, 8.40 and 8.41.

**Table 8.23:** Stability studies of best formulation (LF3)

| Characteristic | Initial | 1st Month | 2nd Month | 3rd Month |
|---|---|---|---|---|
| **Hardness ($kg/cm^2$)*** | 08.10±0.39 | 08.00±0.50 | 07.83±0.29 | 07.67±0.29 |
| **Drug content (%)*** | 99.11±0.53 | 99.01±0.44 | 98.92±0.39 | 98.76±0.56 |
| ***In vitro* drug release at the end of 12 hours*** | 81.28±1.23 | 81.20±0.96 | 81.12±0.76 | 81.09±0.54 |

*All the values were expressed as mean± S.D., n=3.

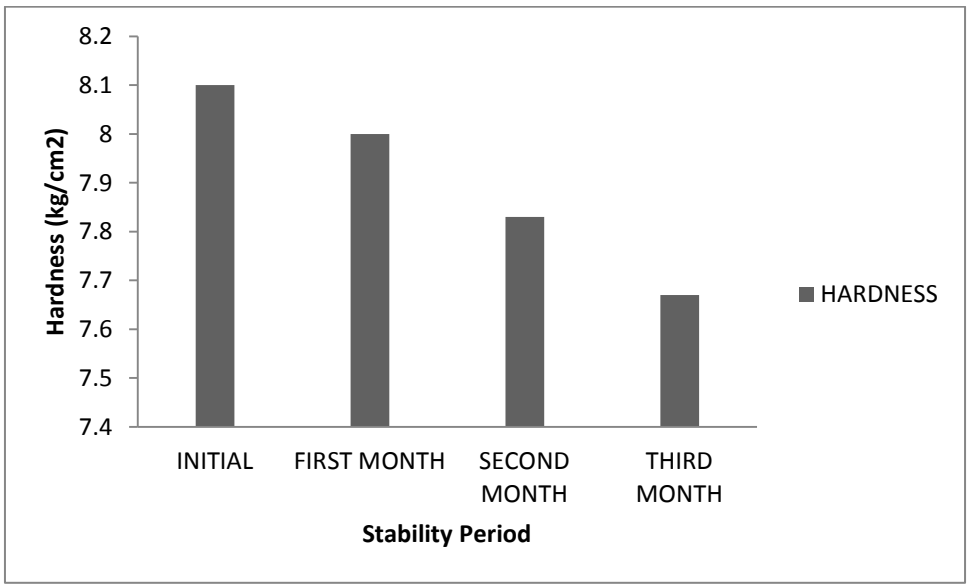



**Figure 8.39:** Comparison for hardness before and after stability studies of best formulation LF3.

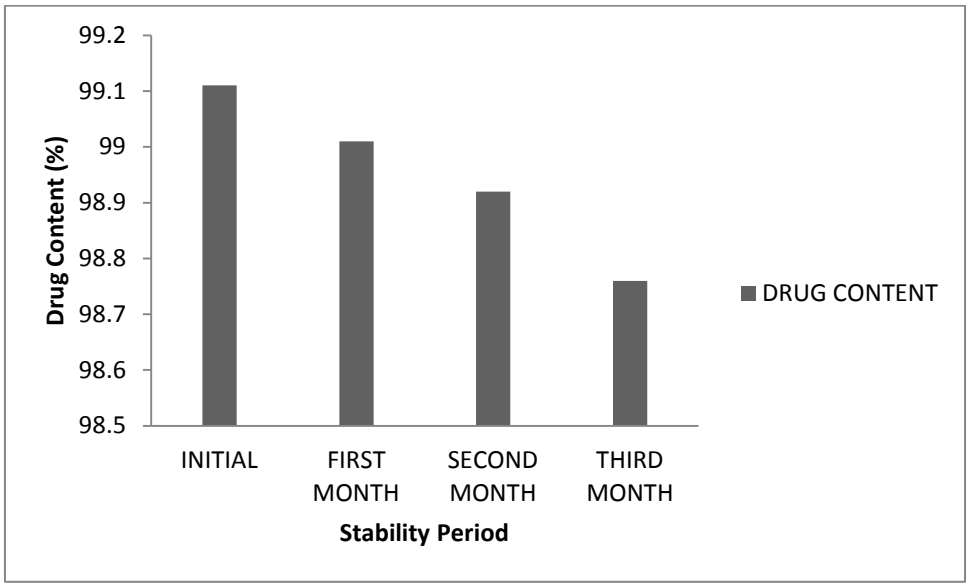



**Figure 8.40:** Comparisons for drug content of before and after stability studies of best formulation LF3.

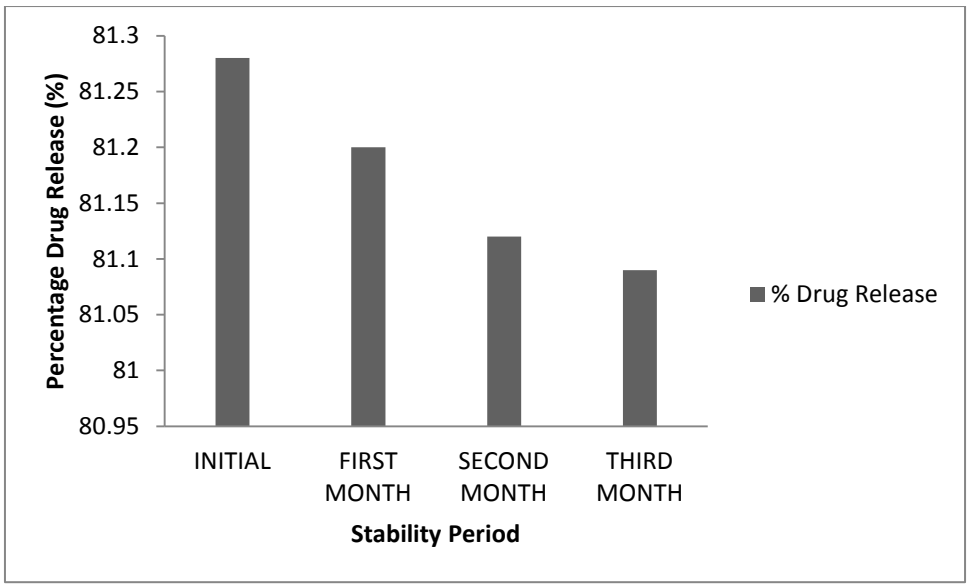



**Figure 8.41:** Comparisons for *in vitro* drug release profile of before and after stability studies of best formulation LF3.

From the above studies there was no significance differences was initiate between the evaluated data from initial and after stability studies and all the values were found in worth accepting limits. The best formulation was showed adequate physical stability at $40^{o}C \pm 2^{o}C$ at 75% ± 5% relative humidity.

# SUMMARY AND CONCLUSION

# 9. SUMMARY AND CONCLUSION

Oral route has been the commonly adopted and most convenient route for the drug delivery. Oral route of administration has been received more attention in the pharmaceutical field because of the more flexibility in the designing of dosage form than drug delivery design for other routes. The oral route of delivery is perhaps the least invasive method of delivering drugs, it's a route that the patient understand and accepts, patient are able to administer the medicine to themselves. For the manufacturer, solid oral dosage form offer many advantages; are generally the most stable forms of drugs, are compact and their appearance can be modified to create brand identification.

Lamivudine was chosen as a drug having soluble in intestinal pH. Lamivudine plays a major role in treatment of HIV infection. It acts as a nucleoside reverse transcriptase inhibitor. The drug half-life in plasma is 6 hours. It is bound to plasma proteins less than 36%. Lamivudine is rapidly absorbed with a bioavailability of over 80% following oral ingestion, hence it was considered as an good candidate for the design of oral sustained release dosage form.

In the present study, an attempt was made to formulate the oral sustained release matrix tablets of lamivudine to provide a dosage form for prolonged period of time, in order to improve efficacy, reduce the frequency of total dose and better patient compliance. Infrared spectroscopy and differential scanning calorimetric analysis confirmed the absence of any drug polymer interaction.

The sustained release matrix tablets were prepared by the direct compression method using different polymers like hydroxypropyl methylcellulose, methylcellulose and ethylcellulose as release retardant polymers. The powders were evaluated for angle of repose, bulk density, compressibility index and hausner's ratio. All the tests revealed that powders showed excellent flow properties.

The resulting monolithic tablets were evaluated for thickness, diameter, weight variation test, hardness, friability and drug content. All the tablet formulations showed acceptable pharmacotechnical properties and complied with pharmacopoeial standards. The *in vitro* release profiles from tablets of drug and different polymer ratio were applied on various kinetic models. *In vitro* release studies revealed that the release rate was decreased with increase in polymer proportion.

In the present studies, matrix formulation LF3 containing HPMC K4M were probably showing maximum retardation of drug release and it shows anomalous diffusion mechanism, for these reasons, it was considered that the formulation LF3 as best formulation among all the nine formulations. Based on release exponent (n) values, it was concluded that mechanism of drug release was found to be diffusion coupled with erosion (anomalous transport mechanism).

From the stability studies, there was no significance difference in hardness, drug content and *in vitro* release profile for the best formulation.

# FUTURE PROSPECTS

# 10. FUTURE PROSPECTS

In the present work, the sustained release matrix tablets of lamivudine were prepared by direct compression technique using synthetic polymers like hydroxypropyl methylcellulose, methylcellulose and ethylcellulose as release retardant polymers.

In this work, only physiochemical characterization such as angle of repose, Carr's index, hausner ratio, weight variation, hardness, thickness, friability, drug content and *in vitro* evaluation of matrix tablet of lamivudine was performed. Along with *in vitro* studies, *in vivo* studies of drug is most important.

In future *in vivo* studies are required to set the *in vitro* - *in vivo* correlation (IVIVC) which is necessary for development of successful formulation and also long term stability studies are necessary.

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# Formulation and evaluation of lamivudine sustained release matrix tablets using synthetic polymers

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## ABSTRACT

The present investigation is aimed at formulating and evaluating sustained release matrix tablets of Lamivudine using different synthetic polymers such as Hydroxypropylmethylcellulose (HPMC K4M), Ethyl cellulose and Methyl cellulose taken at 10%, 20% and 30% of the total weight of the tablet. Lamivudine is a potent hydrophilic anti viral agent indicated for treatment of AIDS (Acquired Immunodeficiency Syndrome). The sustained release tablets were prepared by direct compression method. The powders for tableting were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and hausner's ratio etc.The powder blend showed satisfactory flow properties.The tablets were subjected to thickness, weight variation test, drug content, hardness, friability and in-vitro release studies. All the formulations showed good results which were compliance with Pharmacopoeial standards. In-vitro drug release studies were carried out using USP dissolution apparatus type I at 100 rpm with 900 ml phosphate buffer solutions (PBS) of pH 6.8, maintained at 37±0.5°C. The release kinetics was analyzed using the zero-order, first-order model equation, higuchi's square-root equation, and the Korsmeyer-peppas model. In vitro release studies revealed that the release rate decreased with increases in polymer proportion. The sustained release matrix tablets containing 30% Hydroxypropylmethylcellulose (HPMC K4M) (Formulation LF3) were found to show good initial release (20.41% in two hours) and extended the release upto 12 hours and can overcome the disadvantages of conventional tablets of Lamivudine. The n value obtained from korsmeyer – Peppas model confirmed that the drug release was non- fickian diffusion mechanism.

**Keywords:** Lamivudine, Matrix tablets, Hydroxypropylmethylcellulose, Ethyl cellulose, Methyl cellulose.

## INTRODUCTION

The oral route is the most common route used for administration of drugs. Tablets are the most popular oral solid formulations available in the market and are preferred by patients and physicians alike. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages [1]. Controlled release (CR) tablet formulations are preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase the safety margin for high-potency drugs [2].

Acquired immune deficiency syndrome (AIDS) is a disease of the human immune system caused by the human immunodeficiency virus (HIV). As of 2009, AVERT (also known as the AIDS Education and Research Trust) estimated that there are 33.3 million people worldwide living with HIV/ AIDS, with 2.6 million new HIV infections per year and 1.8 million annual deaths due to AIDS.

When HIV infects a cell, a viral enzyme, reverse transcriptase copies the viral single stranded RNA genome into a double-stranded viral DNA. The viral DNA is then integrated into the host chromosomal DNA, which then allows host cellular processes, such as transcription and translation to reproduce the virus. Reverse Transcriptase Inhibitors blocks the reverse transcriptase's enzymatic function and prevent completion of synthesis of the double-stranded viral DNA, thus preventing HIV from multiplying [3].

Developing oral-sustained release formulations for highly water-soluble drugs with constant rate of release has become a challenge to the pharmaceutical technologists. Fast release drug generally causes toxicity if not formulated as extended release dosage form. Among various formulation approaches, in controlling the release of water-soluble drugs, the development of sustained release coated granules has a unique advantage of lessening the chance of dose dumping which is a major problem when highly water-soluble drug is formulated as matrix tablets. Most of the researchers have worked on matrix tablets and multilayered matrix tablets. In the present study, a sustained release dosage form of Lamivudine has been developed that enables less frequent administering of drug [4].

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The objectives of this work are: (1) to evaluate the physical characters of prepared sustained release tablets, (2) to elucidate the effect of polymer composition, on the release kinetics and (3) to determine the chemical compatibility of formulation containing various ratios of polymer and drug. Lamivudine (ß-L-2', 3'-dideoxy-3'-thiacytidine) (LAM), one of the dideoxycytidine analogue NRTIs, is the first nucleoside analogue approved to treat chronic HBV infection and AIDS [5]. Conventional oral formulations of LAM are administered multiple times a day (150 mg twice daily) because of its moderate half-life ($t_{1/2}$ = 5-7 hours)[6].Treatment of AIDS using conventional formulations of LAM is found to have many drawbacks, such as adverse side effects resulting from accumulation of drug in multi-dose therapy,[3] poor patient compliance, and high cost. Sustained release once-daily formulations of LAM can overcome some of these problems.

## MATERIALS AND METHODS

### Materials

Lamivudine and Methyl cellulose was obtained from Shasun pharmaceuticals, Puducherry. HPMC K4M and ethyl cellulose obtained from Tri star formulation Pvt. Ltd; Puducherry. Poly vinyl pyrrolidone and microcrystalline cellulose was obtained from Nickon laboratories Pvt. Ltd; Puducherry. Magnesium stearate and talc was purchased from Loba chemie Pvt. Ltd; Mumbai. All other chemicals and reagents used were of analytical grade.

### Method

### Direct compression method

The composition of different formulations of lamivudine matrix tablets were

shown in Table 1. Pre weighed ingredients were passed through Sieve no. 60 mesh separately and collected. Ingredients were mixed in geometrical order and thoroughly mixed in a polythene bag for 15 minutes to get a uniform mixture. Talc and magnesium stearate were added to the powder mixture and compressed on a 16- station rotary tablet compression machine using 11mm round flat face punch.

The drug polymer ratio was developed to adjust drug release as per theoretical release profile and to keep total weight of tablet constant for all the fabricated batches under experimental conditions of preparations. The total weight of the matrix tablets was 400 mg with different drug polymer ratios like 1:0.2, 1:0.4, and 1:0.6. The various polymers used were hydroxypropylmethyl cellulose (HPMC K4M), ethyl cellulose and methyl cellulose.

In the formulations prepared, the release retardants included were hydroxypropylmethylcellulose (HPMC K4M), ethyl cellulose and methyl cellulose. Microcrystalline cellulose (MCC) is used as diluent. Magnesium stearate 1% and talc 2 % were used as lubricant and glidant [7].

**Evaluation Parameters**

**Angle of Repose**

The angle of repose of powders was determined by the funnel method. The accurately weighed physical mixture was taken in a funnel. The height of the funnel was adjusted in such a manner that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone measured and angle of repose was calculated using the following equation.

$\tan\theta = h/r$

where h and r are the height and radius of the powder cone, ? is the angle of repose.

**Loose Bulk Density (LBD)**

An accurately weighed powders from each formulation was lightly shaken to break any agglomerates formed and it was introduced in to a measuring cylinder. The volume occupied by the powders was measured which gave bulk volume. The loose bulk density (LBD) of powders was determined using the following formula.

**Loose bulk density = Total weight of powders / Total volume of powders**

**Tapped bulk density (TBD)**

An accurately weighed powders from each formulation was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The TBD of powders was determined by the following formula.

**Tapped bulk density= Total weight of powders / Tapped volume**

**Carr's Compressibility Index**

It is a simple index that can be determined on small quantities of powders. In theory, the less compressible a material the more flowable it is. The compressibility index of the powders was determined using following formula [8].

**Carr's Compressibility Index (%) = [(TBD-LBD)/ TBD] x100**

Where, TBD = Tapped Bulk Density
LBD = Loose Bulk Density

**Hausner's Ratio**

It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to interparticle friction and, as such, could be used to predict powder flow properties[9]. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index. And greater than 1.5 indicates that poor flow, in between these values passable.

**Evaluation of tablets**

**Appearance**

The tablets were visually observed for capping, chipping, and lamination.

**Dimension (Thickness and Diameter)**

The thickness and diameter of tablets were important for uniformity of tablet size. The thickness and diameter of the tablets was determined using a Vernier caliper. Ten tablets from each type of formulation were used and average values were calculated.

**Tablet Hardness**

For each formulation, the hardness of 10 tablets was determined using the Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm$^2$. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg/cm$^2$.

**Percent Friability**

Friability is the measure of tablet strength. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of preweighed tablets was placed in Roche friabilator which was then operated for 100 revolutions. The tablets were then dedusted and reweighed. A loss of less than 1 % in weight is generally considered acceptable. Percent friability (% F) was calculated as follows.

**Friability = 100 X (1-W2/W1)**

Where, W1: Initial weight before friabilator
W2: Final weight after friabilator.

**Weight Variation**

To find out weight variation 20 tablets of each formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight. The test was performed according to the official method [8].

**Drug Content**

Twenty tablets were powdered in a mortar. An accurately weighed quantity of powdered tablets equivalent to100 mg of lamivudine was extracted with pH 6.8 phosphate buffer and the solution was filtered through whatmann filter paper. The absorbance was measured at 271.5 nm after suitable dilution [10].

**In -Vitro Drug Release Characteristics**

Drug release was assessed by dissolution test under the following conditions: n = 3, USP type I dissolution apparatus (Basket method) at 100 rpm in 900 mL of phosphate buffer pH 6.8 throughout the dissolution up to 12 hours, maintained at 37°C ± 0.5°C. An aliquot (5mL) was withdrawn at specific time intervals and replaced with the same volume of pre warmed (37°C ± 0.5°C) fresh dissolution medium. The samples withdrawn were filtered

through whatmann filter paper and drug content in each sample was analyzed by UV-Visible spectrophotometer at 271.5 nm [11].

### Drug Release Kinetics

Data obtained from dissolution studies were fitted to various kinetic equations. The kinetic models used were zero order(cumulative percentage of drug released vs time), first order (log cumulative percentage of drug remaining vs time), Higuchi's (cumulative percentage of drug released vs square root of time) and Korsmeyer (log cumulative percentage of drug released vs log time) equation [12]. The data were fitted into the PCP disso V3 software to find out $R^2$ value.

## RESULT AND DISCUSSION

The prepared sustained release tablets were evaluated for thickness, weight variation, hardness, friability, drug content and in-vitro drug dissolution studies. All the studies were performed in triplicate, and results are expressed as mean ± SD.

### Characterization of powder blend

The powders prepared for compression of sustained release tablets were evaluated for their flow properties, the results were shown in Table 2. Angle of repose was in the range of 21.48±0.17° to 23.93±0.77° which indicates excellent flow of the powder for all formulations. The bulk density of the powder formulation was in the range of 0.455±0.00 to 0.500±0.00 g/ml; the tapped density was in the range of 0.526±0.00 to 0.556±0.00 g/ml, which indicates that the powder was not bulky. The Carr's index was found to be in the range of 10.000±0.00 to 14.286±0.00, the hausner ratio was found to be in the range of 1.11±0.00 to 1.17±0.00, indicating compressibility of the tablet blend is good. These values indicate that the prepared powders exhibited good flow properties.

### Evaluation of matrix tablets

The lamivudine matrix tablets were white, smooth, and round, biconcave shaped in appearance. The results of physicochemical characterizations are shown in Table 3. The thickness of matrix tablets was measured by vernier caliper and was ranged between 4.46±0.05 and 4.55±0.07 mm for all formulation. The weight variation for different formulations (LF1 to LF9) was found to be 0.299±0.22% to 0.657 ± 0.43%, showing satisfactory results as per Indian Pharmacopoeia (IP) limit. The hardness of the matrix tablets was measured by Monsanto tester and was controlled between 7.35±0.67 and 8.10±0.39 kg/cm$^2$. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. The percentage of drug content for LF1 to LF9 was found to be in between 98.48±0.52 to 100.90±0.45 % of Lamivudine, it complies with official specifications.

### In- vitro release study

In-vitro dissolution studies of all the formulations of matrix tablets of Lamivudine were carried out in pH 6.8 phosphate buffer solution. The study was performed for 12 hours, and percentage drug release was calculated at 1 hour time intervals. The results of in-vitro dissolution studies of all formulations were shown in Figure1. The lower initial drug dissolution was observed in tablets containing HPMC K4M (LF3), methyl cellulose (LF6) and ethyl cellulose(LF9). This showed that in high concentration polymers in the presence of pH 6.8 phosphate buffer solution. The variation in drug release was due to different types of polymers and different concentrations of polymer in all the nine formulations. It is expected that the developed formulation should have the following theoretical drug release profile. The drug released from formulation LF1 toLF3 containing HPMC K4M at three concentration levels of 10%, 20%, 30% were found to be 92.56±1.85, 89.57 ± 0.63, and 81.28 ± 1.23% for Lamivudine respectively. The drug released from formulation LF4 to LF6 containing methyl cellulose at three concentration levels of 10%, 20%, 30% were found to be 96.63 ± 1.05, 93.52 ± 0.63 and 89.95 ± 0.82% for Lamivudine respectively. The drug released from formulation LF7 to LF9 containing ethyl cellulose at three concentration levels of 10%, 20%, 30% were found to be 94.71 ± 0.81, 91.26 ± 0.98 and 86.92 ± 0.70% for Lamivudine respectively at the end of 12 hours.

**Table 1:Composition of Lamivudine matrix tablet**

| Ingredients(mg/tablet) | LF1 | LF2 | LF3 | LF4 | LF5 | LF6 | LF7 | LF8 | LF9 |
|---|---|---|---|---|---|---|---|---|---|
| Lamivudine | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |
| HPMC K4M | 40 | 80 | 120 | - | - | - | - | - | - |
| Methyl cellulose | - | - | - | 40 | 80 | 120 | - | - | - |
| Ethyl cellulose | - | - | - | - | - | - | 40 | 80 | 120 |
| Microcrystalline- cellulose pH 102 | 128 | 88 | 48 | 128 | 88 | 48 | 128 | 88 | 48 |
| Polyvinyl pyrrolidone-k30 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| Magnesium stearate | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Talc | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Total weight | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 |

**Table 2:Flow properties of powders**

| Formulation code | Angle of repose (°)* | Loose bulk density(g/ml)* | Tapped bulk density(g/ml)* | Hausner ratio* | Carr's index (%)* |
|---|---|---|---|---|---|
| LF1 | 22.19±0.98 | 0.455±0.00 | 0.526±0.00 | 1.16±0.00 | 13.636±0.00 |
| LF2 | 21.48±0.17 | 0.500±0.00 | 0.556±0.00 | 1.11±0.00 | 10.000±0.00 |
| LF3 | 22.36±0.98 | 0.500±0.00 | 0.556±0.00 | 1.11±0.00 | 10.000±0.00 |
| LF4 | 23.44±0.73 | 0.455±0.00 | 0.526±0.00 | 1.16±0.00 | 13.636±0.00 |
| LF5 | 23.05±0.19 | 0.476±0.00 | 0.556±0.00 | 1.17±0.00 | 14.286±0.00 |
| LF6 | 22.30±0.17 | 0.455±0.00 | 0.526±0.00 | 1.16±0.00 | 13.636±0.00 |
| LF7 | 23.93±0.77 | 0.476±0.00 | 0.556±0.00 | 1.17±0.00 | 14.286±0.00 |
| LF8 | 23.20±0.61 | 0.455±0.00 | 0.526±0.00 | 1.16±0.00 | 13.636±0.00 |
| LF9 | 22.49±0.36 | 0.455±0.00 | 0.526±0.00 | 1.16±0.00 | 13.636±0.00 |

**All the values are expressed as mean± SE, n=3.*

**Table 3: Physico-chemical characterization of Lamivudine matrix tablets**

| Formulation code | Thickness (mm)* | Hardness (kg/cm$^2$)* | Friability (%) | Weight variation (%) | Drug content (%w/w)** |
|---|---|---|---|---|---|
| LF1 | 4.55±0.07 | 8.05±0.44 | 0.150 | 400.4±1.50 | 99.87±0.28 |
| LF2 | 4.46±0.07 | 7.95±0.37 | 0.099 | 402.15±2.94 | 98.48±0.52 |
| LF3 | 4.50±0.07 | 8.10±0.39 | 0.050 | 400.9±2.73 | 99.11±0.53 |
| LF4 | 4.46±0.05 | 7.75±0.42 | 0.075 | 401.25±3.57 | 99.45±0.92 |
| LF5 | 4.49±0.06 | 8.05±0.44 | 0.124 | 402.2±3.61 | 100.08±0.45 |
| LF6 | 4.52±0.04 | 8.00±0.58 | 0.100 | 401.75±2.22 | 99.40±0.31 |
| LF7 | 4.54±0.10 | 7.55±0.55 | 0.087 | 400.8±3.24 | 100.15±0.43 |
| LF8 | 4.49±0.07 | 7.35±0.67 | 0.050 | 403.05±3.12 | 100.90±0.45 |
| LF9 | 4.51±0.06 | 8.05±0.44 | 0.100 | 402.95±2.28 | 98.93±0.86 |

**All the values are expressed as mean± SE, n=10;*
***All the values are expressed as mean± SE, n=3.*

**Table 4: Different Kinetic models for Lamivudine matrix tablets (LF1 to LF9)**

| F. Code | Zero order $R^2$ | First order $R^2$ | Higuchi $R^2$ | Korsemeyer- $R^2$ | Peppas n | Best fit model |
|---|---|---|---|---|---|---|
| LF1 | 0.978 | 0.918 | 0.970 | 0.987 | 0.720 | Peppas |
| LF2 | 0.988 | 0.895 | 0.950 | 0.989 | 0.749 | Peppas |
| LF3 | 0.988 | 0.927 | 0.945 | 0.992 | 0.759 | Peppas |
| LF4 | 0.981 | 0.849 | 0.967 | 0.986 | 0.698 | Peppas |
| LF5 | 0.986 | 0.890 | 0.962 | 0.989 | 0.731 | Peppas |
| LF6 | 0.989 | 0.899 | 0.955 | 0.990 | 0.743 | Peppas |
| LF7 | 0.983 | 0.888 | 0.967 | 0.987 | 0.726 | Peppas |
| LF8 | 0.988 | 0.892 | 0.957 | 0.989 | 0.736 | Peppas |
| LF9 | 0.989 | 0.922 | 0.955 | 0.990 | 0.759 | Peppas |

**Table 5: $t_{50\%}$ drug release of formulation LF1 to LF9**

| Parameter | Formulation code LF1 | LF2 | LF3 | LF4 | LF5 | LF6 | LF7 | LF8 | LF9 |
|---|---|---|---|---|---|---|---|---|---|
| $t_{50\%}$(hrs) | 5.2 | 6.3 | 8.0 | 5.3 | 5.8 | 6.2 | 5.3 | 6.0 | 6.4 |

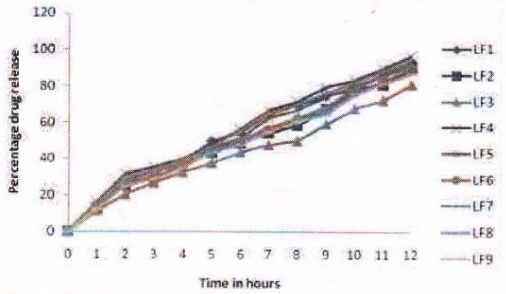


**Figure 1: In-vitro drug release of formulation LF1 to LF9**

The release rate from the HPMC K4M polymer was found to be less as compared to Ethyl cellulose and methyl cellulose. This might be due to slow erosion of matrix and its property which retard the drug release from the tablet for long duration.

The regression coefficient obtained for formulation LF1 to LF9 korsmeyer peppas kinetics were found to be higher ($R^2$: 0.986 to 0.992) when compared with other kinetic models (first order, zero order, higuchi). The results were shown in Table 4. Drug release data was also fitted to peppas model, which showed the slope (n) value (0.698 to 0.759), indicating a anomalous diffusion release mechanism. Lamivudine exhibited anomalous diffusion as dominated mechanism for optimized formulation (LF3).

Based on the *In- vitro* drug release data, the $t_{90\%}$ was calculated and the results given in the Table 5. From this data, the formulation LF3 showed the maximum retardation of drug release and it shows anomalous diffusion mechanism, for these reasons, it was considered that the formulation LF3 was best formulation among all the nine formulations.

## CONCLUSION

This study deals with the investigation carried out with the objective of developing oral sustained release formulation of Lamivudine using Hydroxypropylmethylcellulose, Ethyl cellulose and Methyl cellulose. Preparation of matrix tablet by direct compression technique was found to be more effective in sustaining the release of drug. Drug content for all formulations were found to be complies with pharmacopoeial standards. Formulation LF3 containing HPMC K4M with hardness 8.1 kg/cm$^2$.The controlled and efficient drug delivery system developed in the present study will maintain the plasma Lamivudine levels better, which will overcome the drawbacks associated with the conventional therapy. The kinetics of drug release was optimized formulation explained by peppas equation. The drug release from the tablets was sufficiently sustained and anomalous diffusion mechanism of the drug from tablets was confirmed. Based on the in-vitro drug release data, the formulation LF3 it was concluded as best formulation. In conclusion the present study demonstrated the successful preparation of sustained release matrix tablet of Lamivudine.

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